Development and Applications of Palladium(0)-Catalyzed-C(sp^3)-H Activation

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Development and Applications of Palladium(0)-catalyzed-C(sp^3)-H Activation

Abstract

Over the last decade, the transition metal-catalyzed intramolecular activation of unactivated C-H bonds has emerged as a powerful method to transform otherwise inert entities allowing access to molecular complexity in an atom- and step-economical fashion.

Research in our group is centered on the activation and functionalization of C(sp^3)-H bonds that lead to the development of new methodologies and applications including asymmetric catalysis, mechanistic studies and total synthesis of complex molecules.

Recently, our group developed a straightforward access to hexahydroindoles scaffolds by intramolecular C(sp^3)-H alkenylation. As a follow-up, we first investigated the application of this new methodology in combination with a directed C(sp^3)-H arylation to achieve a collective synthesis of aeruginosins.

In a second part, we extended this methodology to the development of a modular C(sp^3)-H alkenylation for the synthesis of a wide variety of γ -lactams, which are prevalent scaffolds found in numerous bioactive natural molecules.

Finally, we developed a highly efficient synthesis of β-lactams, which are valuable compounds widely used in pharmaceutical chemistry, by palladium(0)-catalyzed-C(sp^3)-H carbamoylation.

Keywords : C-H functionalization, C-H activation, organometallic catalysis, palladium, total synthesis, aeruginosins, γ-lactams, β-lactams

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Published works during the Ph.D.

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A General and Scalable Synthesis of Aeruginosin Marine Natural Products Based on Two Strategic C(sp^3)-H Activation Reactions. Dailler, D.‡; Danoun, G.‡; Baudoin, O., *Angew. Chem. Int. Ed.* **2015,** *54*, 4919. *"Highlighted in Synfact"*

‡ : co-authors

Abbreviations

Ac	Acetyl
Ad	Adamantyl
Ar	Aryl
API	Active Pharmaceutical Ingredient
BCB	Benzocyclobutene
BDE	Bond Dissociation Energy
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
cat.	catalytic
Cbz	Carboxybenzyl
Choi	2-Carboxy-6-hydroxyoctahydroindole
CMD	Concerted Metalation-Deprotonation
COD	1,4-Cyclooctadiene
Cogen	9-Methylfluorene-9-carbonyl chloride
Cy	Cyclohexyl
Cyp	Cyclopentyl
dba	Dibenzylideneacetone
DIBAL-H	Diisobutylaluminium hydride
DCE	1,2-dichloroethane
DCM	Dichloromethane
DFT	Density functional theory
DHIQ	Dihydroisoquinolines
DIPEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMAc	*N*,*N*-Dimethylacetamide

DMF	*N*-*N*-dimethylformamide
DMS	Dimethyl sulfide
DMSO	Dimethylsulfoxide
d.r.	Diastereoisomeric ratio
EDCI	*N*′-Ethylcarbodiimide hydrochloride
equiv.	equivalent
EOM	Ethoxymethyl
Et	Ethyl
e.r.	Enantiomeric ratio
FG	Functional Group
F-TOTP	tri(5-fluoro-2-methylphenyl)phosphine
GCMS	Gas chromatography coupled with mass spectrometry
HBTU	(2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate)
HLF	Hofmann-Löffler-Freytag
HMDS	Hexamethyldisilazane
HPLA	Hydroxyphenyllactic acid
HPLC	High pressure liquid chromatography
*i*BAD	Intramolecular base-assisted deprotonation
IBCF	Isobutyl chloroformate
i-Pr	2-Propyl
L	Ligand
Me	Methyl
MOM	Methoxymethyl
MS	Molecular sieve
NBE	Norbornene
n-Bu	1-Butyl

NHCs	*N*-heterocyclic carbenes
NMM	*N*-Methylmorpholine
NMR	Nuclear magnetic resonance
PG	Protecting group
Ph	Phenyl
PIP	2-pyridinylisopropyl
Piv	Pivaloyl
Pr	Propyl
Py	Pyridine
PyBOP	Benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
RT	Room temperature
SEM	[2-(trimethylsilyl)ethoxy]methyl]
SM	Starting Material
TADDOL	*α,α,α′,α′*-Tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol
TBAF	Tetrabutylammonium fluoride
t-Bu	*tert*-Butyl
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TEBAC	Benzyltriethylammonium chloride
Tf	Triflyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMB	Trimethoxybenzyl
TMS	trimethylsilyl

TOTP Tri-*o*-tolylphosphine

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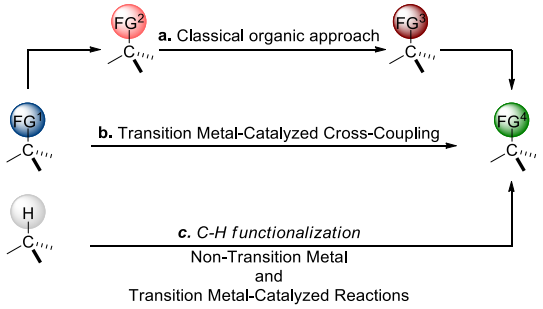
Chapter 1

Bibliographic part

1. Generality

Organic chemistry started in the nineteenth century with the synthesis of urea by Friedrich Wöhler in 1828 and of the mauveine by Henry Perkin in 1856, which led to the rise of both the chemical industry and academic research[1]. Since the emergence of organic chemistry, classical approaches used by chemists to build and/or functionalize organic compounds consisted in transforming pre-existing functional groups into the desired chemical functions. This strategy can solve many regio- and/or chemoselectivity issues by using the impressive catalogue of organic reactions and a well-designed synthetic route. However, the need of prefunctionnalized starting materials which are often obtained after several transformations has prompted chemists to investigate more atom and step economical alternatives (Scheme 1 a.).



Scheme 1 : *Overview of different approaches to functionalize organic compounds*

Over the past decades, transition metal catalysis has witnessed a rapid and comprehensive development. Notably, palladium-catalyzed cross-coupling emerged as a powerful tool for carbon-carbon bond formation. Indeed, this synthetic approach allowed new disconnections for synthetic chemists from academia and industry to access molecular complexity in a rapid, convenient and selective fashion (Scheme 1 b.). This is emphasized by the continuously growing literature in this field (Figure 1) and the attribution of the Nobel Chemistry Prize to Heck, Negishi and Suzuki in 2010[2].

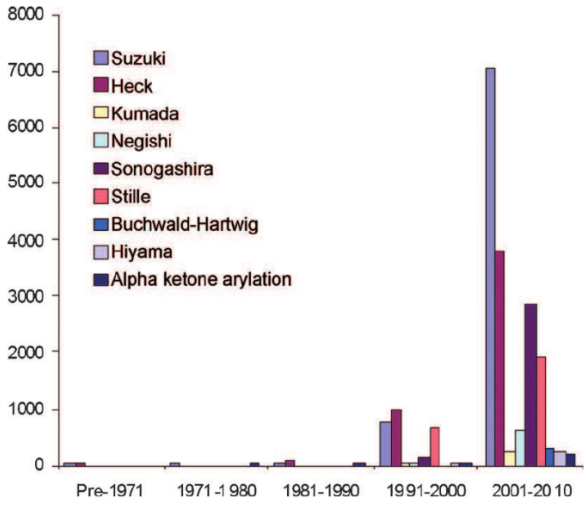
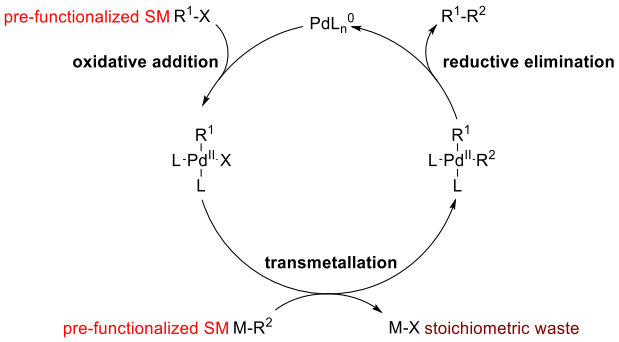


Figure 1 : *Growth in the number of publications and patents on named metal-catalyzed cross-coupling reactions*

Such palladium-catalyzed cross-coupling reactions are initiated by the oxidative addition of a Pd(0) complex into a carbon-halide/pseudohalide bond generating an electrophilic Pd(II) organometallic species, which then undergoes transmetallation with a nucleophilic organometallic compound. The resulting Pd(II) complex affords the desired cross-coupled compound after reductive elimination (Scheme 2). Various advantages were offered by this catalytic system in terms of retrosynthetic analysis[3], step-economy and industrial applications[4]. Nevertheless, some limitations such as the pre-functionalization of starting materials and the production of stoichiometric toxic metal wastes stimulated chemists to turn their attention to direct C-H functionalization.



Scheme 2 : *Simplified general catalytic cycle for palladium-catalyzed cross-coupling reaction*

Indeed, due to the ubiquity of C-H bonds in organic compounds, their direct and selective functionalization provides new strategic and economic benefits for organic chemists, in agreement with the atom economy idea (Scheme 1 c.)[5]. However, C-H functionalization remains challenging due to the intrinsic reactivity of C-H bonds and selectivity issues.

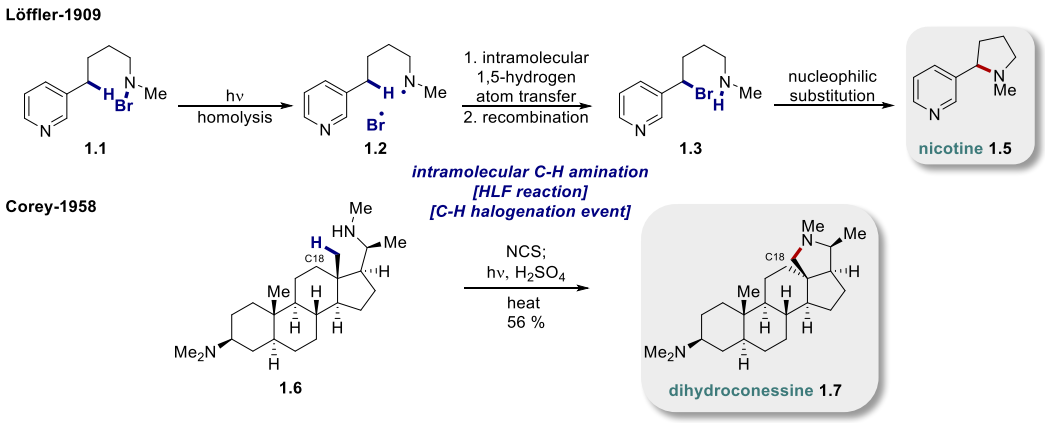
2. C(sp^3)-H bond functionalization in organic synthesis

2.1. Reactivity of aliphatic C-H bonds

For a long time, the functionalization of C-H bonds has been ignored in retrosynthetic analysis due to the relative inertness of these bonds. Aliphatic compounds also known as "parrafins" from the Latin *parum affinis* (without affinity) can be called "noble gases of organic chemistry". Indeed, alkanes such as methane have a high bond dissociation energy (BDE) of 104 Kcal/mol and they are entirely saturated, which means they do not contain π- nor n-electrons allowing classical reactivities[6]. Nevertheless, alkanes can react promptly with extremely active species such as radicals, carbenes and highly acidic compounds[7]. Such reactivities were exploited by scientists in total synthesis of natural products leading to pioneering applications of C-H bonds functionalization. Generally, these strategies relied on the generation of radicals, carbenes or nitrenes in structural proximity to the alkyl groups, thus allowing C-H abstraction or insertion.

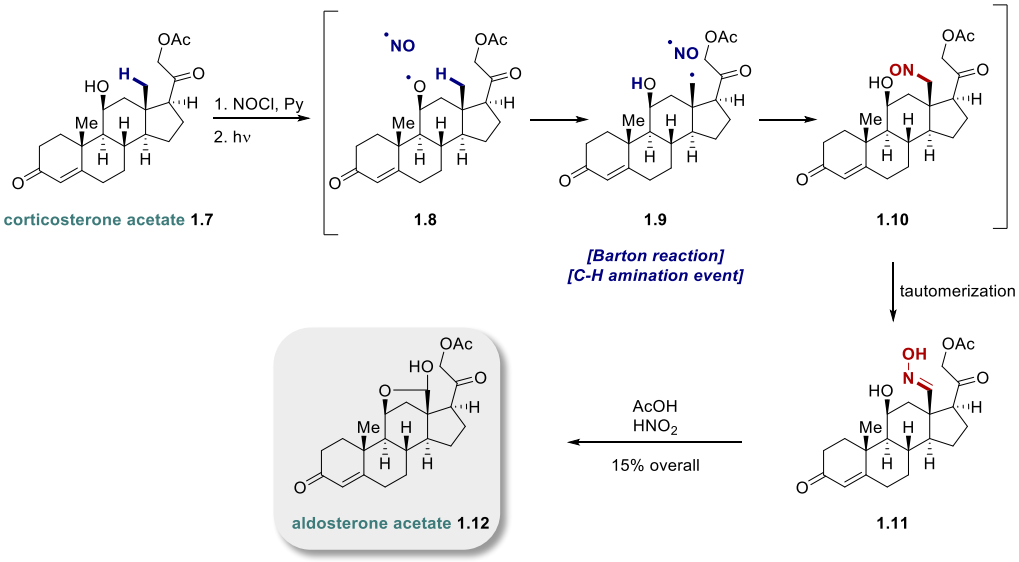
2.2. Early contributions in total synthesis

Early results were obtained by Löffler taking advantage of the photochemical homolysis of *N*-halomamine **1.1** to generate a highly energetic *N*-centered radical **1.2** which affords **1.3** via a 1,5-hydrogen transfer (6-membered transition state) and radical recombination. Finally, the halogen atom is displaced by the secondary amine leading to the synthesis of nicotine (Scheme 3)[8]. Much later, exploiting the same Hofmann-Löffler-Freytag methodology, Corey and Arigoni were independently able to functionalize the unactivated C-18 methyl group of steroid derivatives to provide natural aminosteroids in few steps[9].



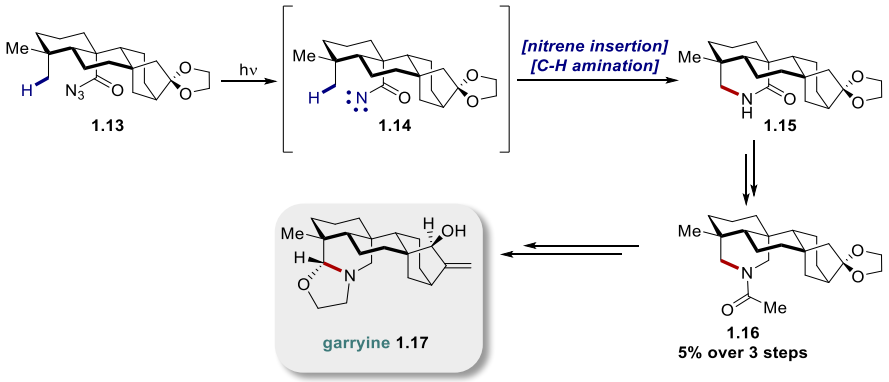
Scheme 3 : *Early total syntheses based on the Hofmann-Löffler-Freytag reaction*

In 1960, Barton and coworkers developed a new photochemical reaction relying on nitrite ester photolysis[10]. Starting from readily available corticosterone acetate **1.7**, they initiated, under photochemical conditions, homolysis of the nitrite ester leading to highly reactive *O*-radical **1.8**, which undergoes a selective 1,5-hydrogen transfer to afford **1.9**. This latter recombines with the nitroxyl radical and give **1.11** after tautomerization. Final hydrolysis of the oxime **1.11** leads to aldosterone acetate **1.12** in moderate yield (Scheme 4)[11].



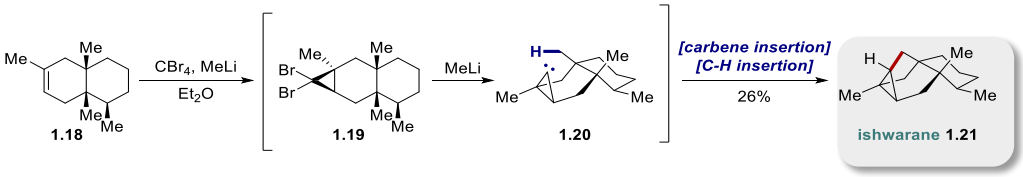
Scheme 4 : *Total synthesis of Aldosterone acetate based on Barton oxydation*

Analogous to radicals, nitrenes and carbenes are highly reactive species able to perform C-H functionalization. In 1964, Masamune and coworkers studied the unstability of acyl azide **1.13** under photoirradiation generating acyl nitrene **1.14**. This latter reacts with the spatially close methyl C-H bonds via a remarkable nitrene insertion to afford C-H amination product **1.15**. After further transformations, garryine **1.17** was obtained in low overall yield (Scheme 5)[12].



Scheme 5 : *Total synthesis of garryine based on nitrene insertion*

Exploring the total synthesis of the tetracyclic sesquiterpene ishwarane **1.21**, Cory's group demonstrated the synthetic utility of carbene C-H insertion. Starting from advanced intermediate **1.18**, they prepared diastereoselectively gem-dibromocyclopropane **1.19**, which upon treatment with methyllithium, provided cyclopropylcarbene **1.20**. Carbene C-H insertion takes place with the most accessible methyl C-H bond to give in low yield a concise 6-step total synthesis of ishwarane **1.21** (Scheme 6)[13].



Scheme 6 : *Total synthesis of ishwarane based on carbene insertion*

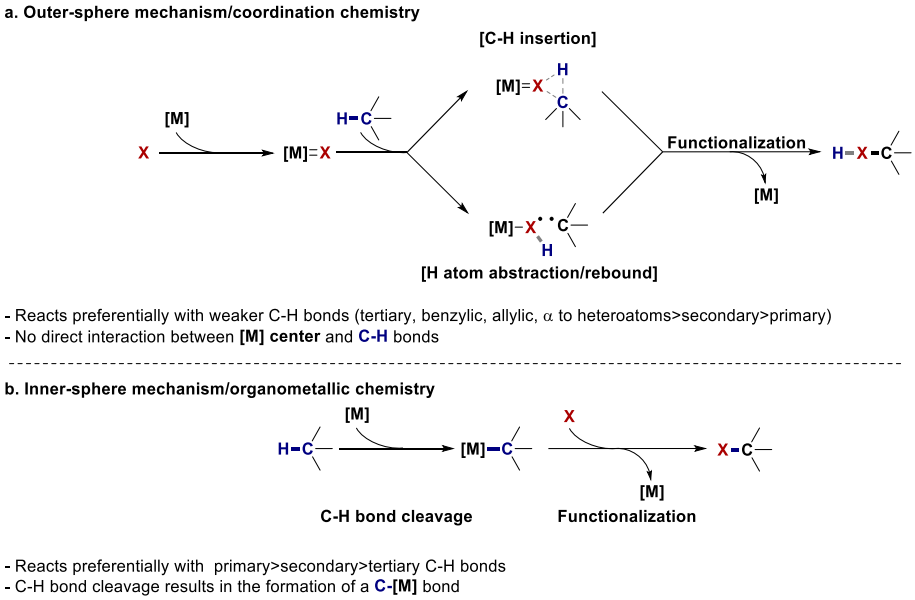
Despite moderate to low yields, these selected pioneering examples highlight the synthetic potential of direct C-H functionalization in total synthesis. However, these advances suffered from a lack of reactivity and generality until the eighties. Nevertheless, these remarkable contributions served chemists as an inspiration for the development of more practical and general C-H bonds functionalization methodologies and their applications in total synthesis[14]. Chemists turned their attention to the study of transition-metal catalysis, based on early organometallic observations[15].

3. Transition metal catalyzed C(sp^3)-H functionalization

3.1. General mechanistic aspect

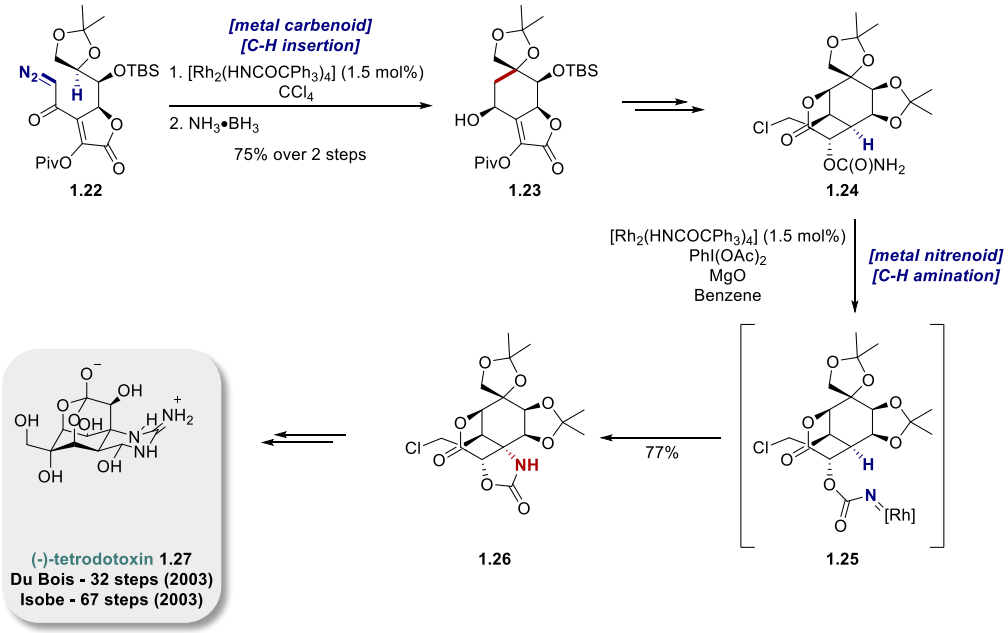
Transition metal catalyzed C(sp^3)-H functionalization processes were subdivided into two different classes based on the C-H bond breaking mechanism involved[16]. Robert Crabtree distinguishes coordination chemistry from the organometallic approach. This was then taken up and labelled by Melanie Sandford as "outer-sphere" and "inner-sphere" mechanisms[17].

In "outer-sphere", the alkane interacts first with a highly-activated ligand of a metal complex (X= carbene[18], nitrene[18c, 19], oxene[7b]) before the C-H bond functionalization event. Two distinct mechanisms can be considered (C-H insertion or H atom abstraction/radical rebound). No formation of a metal-alkyl intermediate is involved. Both pathways show preferential selectivity for weaker C-H bonds (tertiary>secondary>primary) due to the radical and/or cationic character at the carbon center (Scheme 7 a.).



Scheme 7 : *Different approaches for the transition-metal catalyzed C-H functionalization*

Based on transition-metal catalysis, which offers more control over the reaction course due to the modulation of the reactivity of the metal complex by the ligand properties, numerous applications in total synthesis were achieved[14, 20]. One of the most impressive ones is the total synthesis of the structurally complex (-)-tetrodotoxin **1.27** by the group of Du Bois (Scheme 8). Thanks to two key rhodium-catalyzed C-H functionalizations (C-H insertion followed by C-H amination), they have built this functionalized bridged natural product in twice less steps than the previous synthesis, thus highlighting the synthetic power of transition-metal catalyzed C-H functionalization[21].

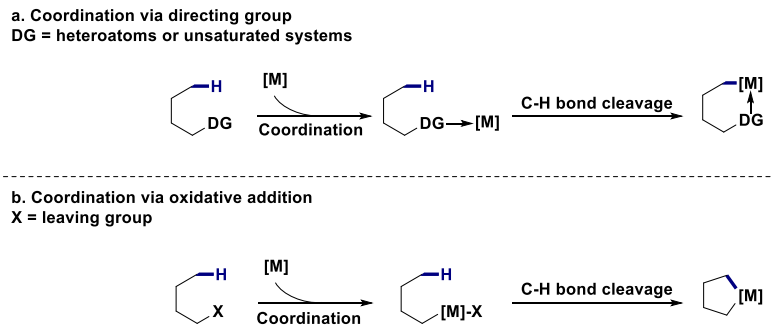


Scheme 8 : *Total synthesis of (-)-tetrodotoxin*

In "inner-sphere", C-H bond breaking generates an organometallic intermediate, which reacts to obtain the functionalized product (Scheme 7 b.). In this mechanism, the C-H bond cleavage event can be called "true C-H activation" as defined by Shilov and Shul'pin and includes reactions involving an agostic interaction between the metal center and the C-H bond prior to C-H activation (via oxidative addition or CMD) leading to an organometallic species[7b, 16, 22]. This approach tends to give a selectivity trend opposite compared to the one observed in "outer-sphere" (C(sp^2)-H>primary>secondary>tertiary). This can be partially explained by looking at the basicity of the C-H bond to activate[23]. In fact, transition metal-catalyzed C(sp^2)-H bonds activations are generally favored over C(sp^3)-H bonds which is in agreement with the higher acidity of aromatic and vinyl protons over aliphatic protons. On the other hand, alkanes do not contain π-electrons allowing π-metal pre-coordination lowering the energy barrier for C−H activation. These combined effects tend to make transition metal-catalyzed C(sp^3)-H activation a more challenging process[24].

3.2. Metalation step

Despite these obstacles, C(sp^3)-H functionalization can be facilitated by pre-complexation strategies. This means that the substrate coordinates to the metal complex prior to the C-H bond breaking event. Indeed, the substrate becomes ligand of the metal, which will modulate their reactivity. Furthermore, it brings the transition metal in close proximity to the targeted C-H bond, thus enhancing selectivity and lowering the activation barrier triggerring the intramolecular C-H activation. First, such coordinations is possible using Lewis basic directing groups such as heteroatoms or unsaturated bonds (mainly L-type ligand) (Scheme 9 a.). On the other hand, oxidative addition of a carbon-leaving group such as halides (I, Br or Cl) or pseudo-halides (OTf) (X-type ligand) to a low valent metal can be used (Scheme 9 b.)[24a].



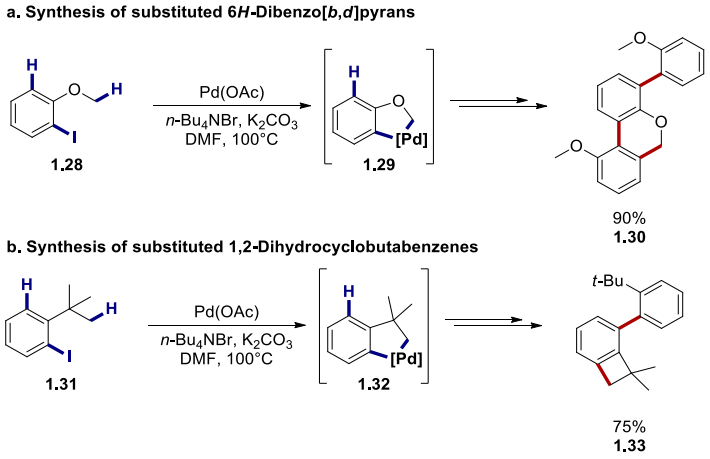
Scheme 9 :*Complexation strategies to trigger aliphatic C-H activation*

Baudoin's group research focuses mainly on Oxidative-Addition-Initiated C(sp^3)-H activation. The next chapters will be devoted to this research area.

4. Oxidative-Addition-Initiated C(sp^3)-H Activation

4.1. Early examples and inspiration

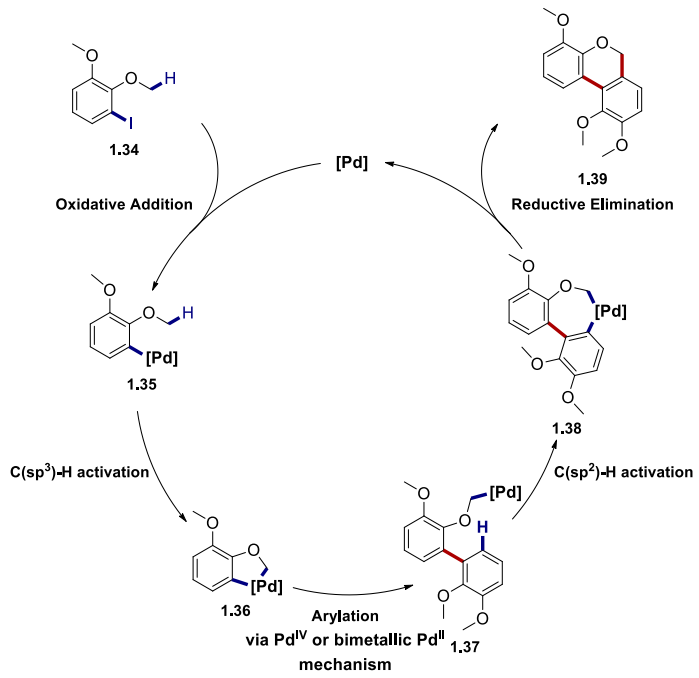
In 1992, Dyker reported a new domino coupling reaction based on the palladium-catalyzed C-H activation of methoxy groups, which was then extended to the activation of *tert*-butyl groups. In both cases, these intramolecular processes led to a simple synthesis of substituted dibenzopyrans[25] and benzocyclobutenes[26] (BCB) based on self-condensation of two or three aryl iodides (Scheme 10).



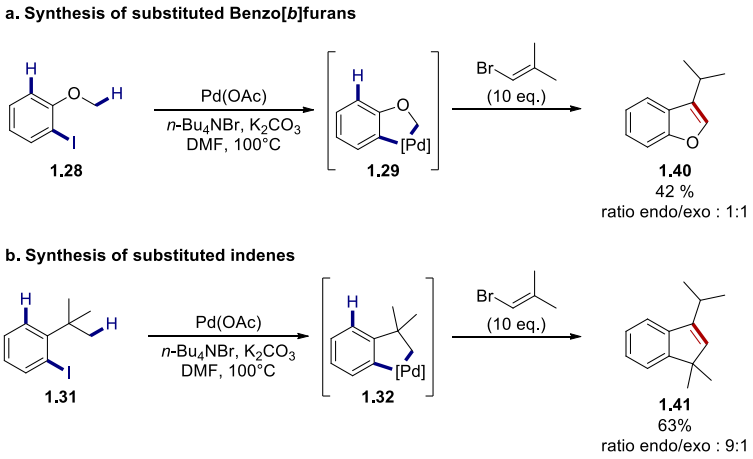
Scheme 10 : *Synthesis of annelated rings by intramolecular C(sp^3)-H activation*

Mechanistically, the catalytic cycle starts with an oxidative addition to **1.35** followed by the intramolecular C(sp^3)-H activation of the proximal methoxy group to afford the five-membered palladacycle **1.36** (Scheme 11). This complex reacts with another equivalent of aryl iodide leading to **1.37**. Based on previous observations[27], this procedure was first reported by Dyker as a Pd^{II}-Pd^{IV}-Pd^{II} process. Theoretical studies by Echavarren & Cardenas tend to indicate that this arylation step go through a bimetallic Pd^{II} mechanism[28]. Finally, intermediate **1.37** is subjected to an intramolecular C(sp^2)-H arylation giving, after reductive elimination, dibenzopyran **1.39**.

As an extension, Dyker thought to use palladacycle intermediates **1.29**, **1.32** or **1.36** wisely. Indeed, he intercepted these palladacycle species with bromoalkenes to develop a new approach for the synthesis of substituted indenes[26] (Scheme 12 a.) and benzofurans[29] (Scheme 12 b.), thus highlighting the synthetic opportunity for organic chemists to consider palladacycles also as reactive intermediates[30].



Scheme 11 : *Proposed mechanism for the formation of dibenzopyrans*



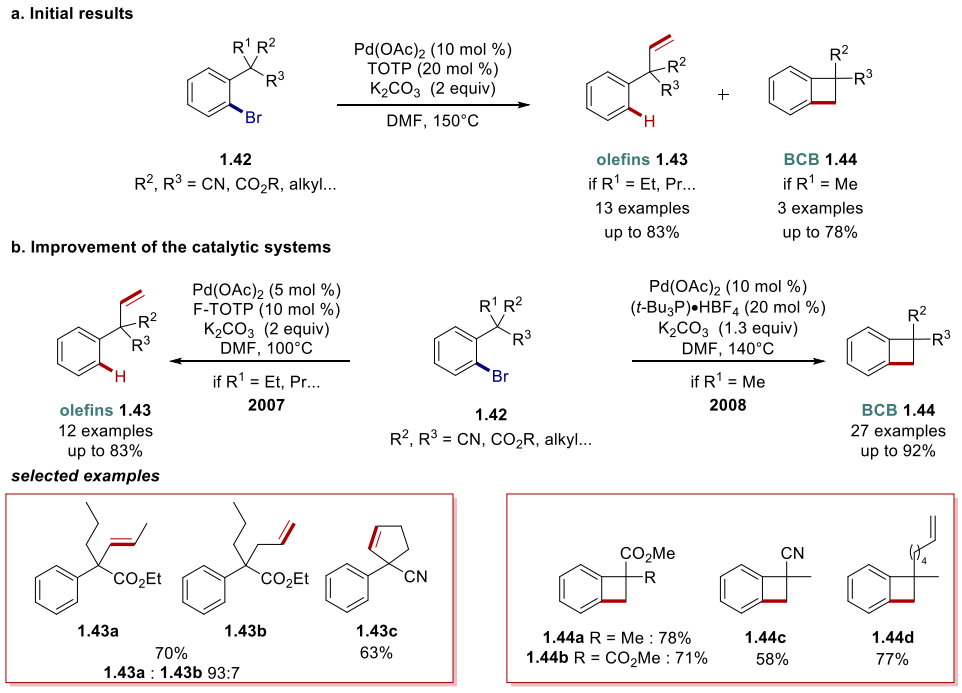
Scheme 12 : *Interception of palladacycle intermediates*

Even though a lack of control on the reaction course was observed in this ligandless palladium catalysis, these results represent a formidable proof-of-concept for palladium-catalyzed C(sp^3)-H activation leading to advanced structures in a limited number of steps. These landmark results are a defining moment for the future development of palladium-catalyzed C(sp^3)-H activation.

4.2. Generalization of Palladium-catalyzed C(sp^3)-H activation

4.2.1. Initial results

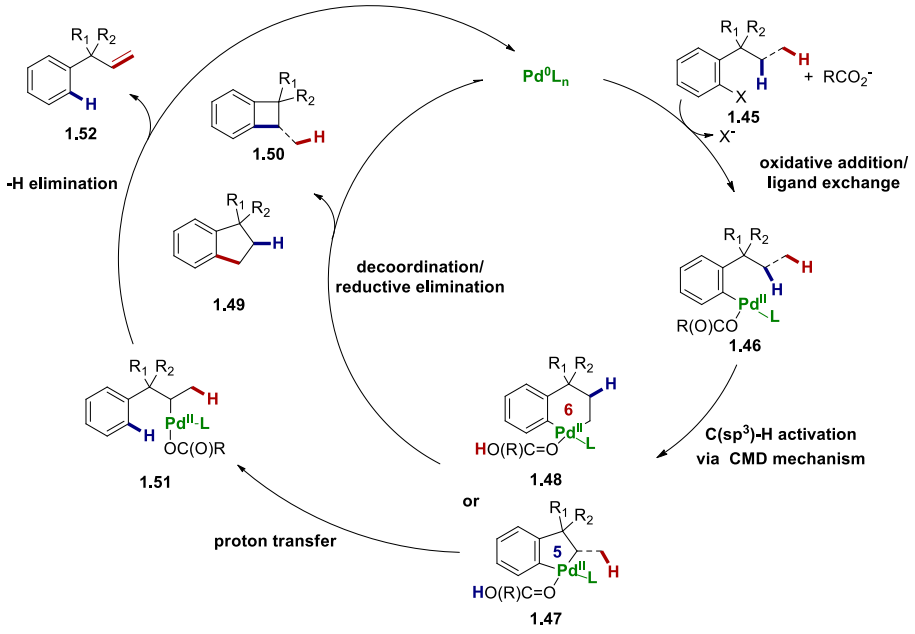
Based on the previous examples described by Dyker, Baudoin and coworkers reported the first example of Pd(0)/ligand-catalyzed intramolecular C(sp^3)-H arylation[31]. Thanks to the use of suitable ligands, they avoided condensation and cross-coupling by-products starting from the same aryl halides than Dyker. Furthermore, depending on the benzylic *gem*-Dialkyl substitutions of starting material **1.42**, two different classes of products were obtained. Indeed, using the same catalytic system based on $Pd(OAc)_2$, potassium carbonate and the sterically demanding tri-*o*-tolylphosphine (TOTP) ligand, both olefins **1.43** and BCB **1.44** were obtained in good yield (Scheme 14 a.). After further studies, they found out that two distinct phosphines could favor each reaction pathway. First, they designed an electron-deficient triarylphosphine ligand (tri(5-fluoro-2-methylphenyl)phosphine : F-TOTP) which provides higher efficiency (reaction operates at 100°C instead of 150°C), selectivity, notably for the disubstituted olefins (*i.e.* TOTP 81:19; F-TOTP 93:7 **1.43a**:**1.43b**) and reactivity for hindered substrates (*i.e.* access to cyclic olefins **1.43c**) and nitriles derivatives (Scheme 13 b.)[32]. On the other hand, they discovered that P*t*Bu$_3$ ligand allows a higher efficiency and a broader scope for the synthesis of BCB as well as the use of aryl chlorides as starting materials[33].



Scheme 13 : *Initials results for Pd(0)/Ligand−Catalyzed Intramolecular C(sp^3)−H Activation*

4.2.2. Mechanistic insights

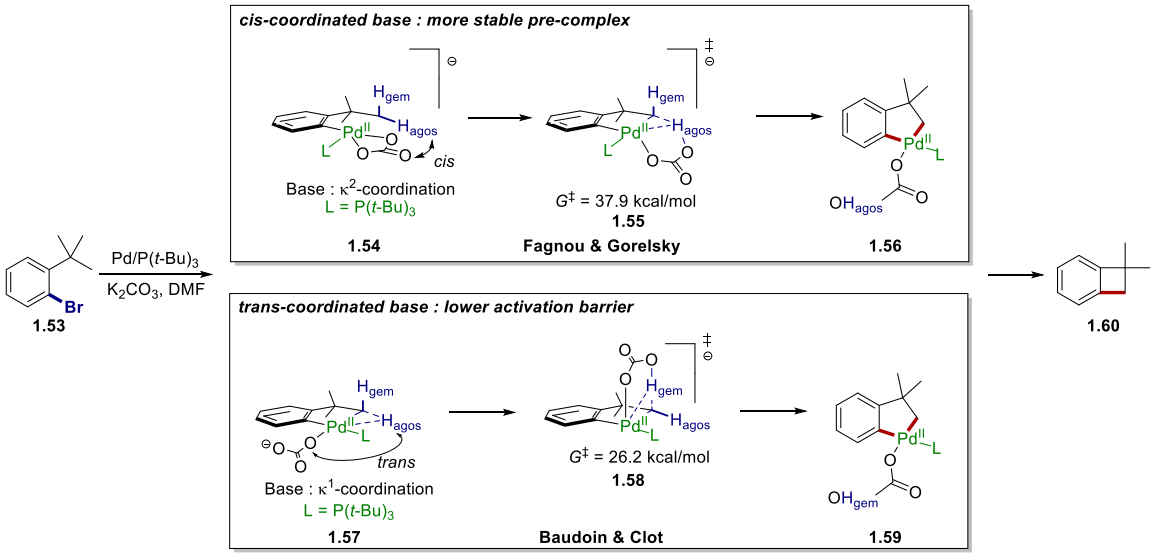
Since the development of transition-metal-catalyzed C(sp^2)-H activation for the synthesis of biaryls, numerous mechanisms have been proposed such as carbopalladation (Heck-type), electrophilic aromatic substitution or σ-bond metathesis[34]. Thanks to experimental and computational studies by Davies & MacGregor[35] and Echavarren & Maseras[36] on the C(sp^2)-H activation, such mechanisms have been excluded. Instead, they described the concerted metalation deprotonation (CMD) mechanism[37]. Then, the groups of Fagnou[38] and Baudoin[33a, 39] have corroborated that this CMD mechanism is also involved in the activation of C(sp^3)-H bonds. The accepted catalytic cycle for this transformation starts with the oxidative addition of a monoligated Pd(0) complex into the carbon-halide or pseudohalide bond of **1.45**. Ligand exchange with a base such as carboxylate or carbonate then generates electrophilic Pd(II) species **1.46**. Depending on the substitution pattern of the precursors of C-H activation, different scaffolds can be built. After the C-H activation step, 5- **1.47**, 6-**1.48** or rarely 7-membered palladacycles were obtained which after decoordination of the base and reductive elimination, generally generate cyclized products such as **1.49-1.50**. On the other hand, olefins can be obtained *via* proton transfer of **1.47** leading to intermediate **1.51**, which then undergoes base-mediated β-hydride elimination to afford olefins **1.52** (Scheme 14).



Scheme 14 : *General mechanism of C(sp^3)-H activation for the synthesis of carbocycles and olefins*

Mechanistically, different pathways for the C(sp^3)-H activation step were studied *via* DFT calculations[39-40]. In 2008, Baudoin & Clot described a complete investigation of the whole mechanism with different ligands and bases for the formation of BCB.

Thanks to preliminary experimental observations, notably a significant kinetic isotope effect (KIE), they were able to fine-tune their study. Notably, they excluded the results computed for PMe_3 instead of P(*t*-Bu)$_3$ or for AcO^- and HCO_3^- instead of CO_3^{2-} which show energy profiles in disagreement with experimental observations (rate-limiting step associated to C-Br oxidative addition). Using the experimental ligand and base system for the BCB formation (*i.e.* bulky P(*t*-Bu)$_3$ and carbonate base) in the calculations, they were able to locate three plausible transition states. Whereas the transition state (TS) for an intermolecular proton abstraction was eliminated due to high activation barrier, which can be imputed to the high entropic cost, two TSs corresponding to an intramolecular proton abstraction seemed to be promising. *Cis*-activation mode proposed by Fagnou & Gorelsky was calculated and occurs *via* a more stable precomplex **1.54** due to favorable κ^2-carbonate coordination. This strong coordination has a significant impact on the energy required to reach the transition state **1.55** (37.9 kcal/mol). On the other hand, *trans*-activation mode proposed by Baudoin & Clot led to the less stable κ^1-precomplex **1.57**. Interestingly, compared to **1.54**, agostic interaction was observed in the precomplex **1.57** which enhances the protic character of the geminal proton. Thanks to this interaction and κ^1-precomplex coordination, a lower activation barrier is required to reach transition state **1.58**. Interestingly, the C-H bond cleaved in this mode is the geminal proton and not the agostic one. Whereas for the BCB **1.60** synthesis, *trans*-coordination mode seems to be the most adequate, both pathways should be considered in mechanistic studies regarding other substrates (Scheme 15).

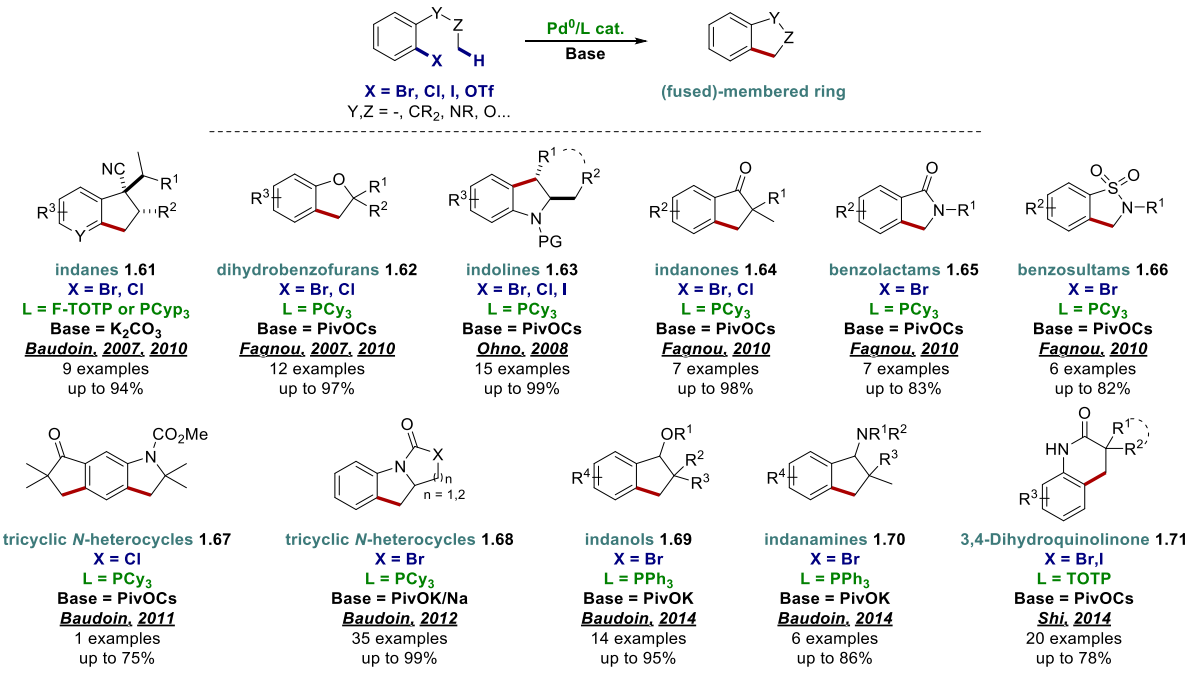


Scheme 15 : *Plausible mechanism for the formation of BCB (B3PW91(DMF))*

Thanks to these computational studies and experimental data, a selectivity guideline for the Pd(0)-catalyzed intramolecular C(sp^3)-H activation can be proposed. This selectivity trend is dominated by several factors. Nevertheless, the size of the palladacycle formed after C-H activation (5-membered>6-membered>>7-membered) as well as the acidity of the cleaved C-H bond (benzylic>aromatic>cyclopropyl>methyl>methylene>methine) are predominant. Other considerations such as steric environment, stability and ring-strain of the product as well as reaction conditions can influence the reaction course. A compromise between all these factors has to be considered when designing new substrates to prevent side-reactions.

4.2.3. Intramolecular activation of unactivated C(sp^3)-H bonds

Inspired by initial works (Scheme 13) and interested by the synthetic potential of such C-H bonds functionalization, some research groups turned their attention to the generalization of the intramolecular activation of unactivated C(sp^3)-H bonds leading to molecular complexity in a step- and atom-economic fashion. Broad varieties of ring systems were accessed and literature in this field is chronologically summarized below (Scheme 16). They are mainly based on 5-membered ring systems (**1.61 to 1.70**) except **1.71**[41]**,** which also allows direct access to *N*-H lactams thanks to the use of non protected precursors (Scheme 16).



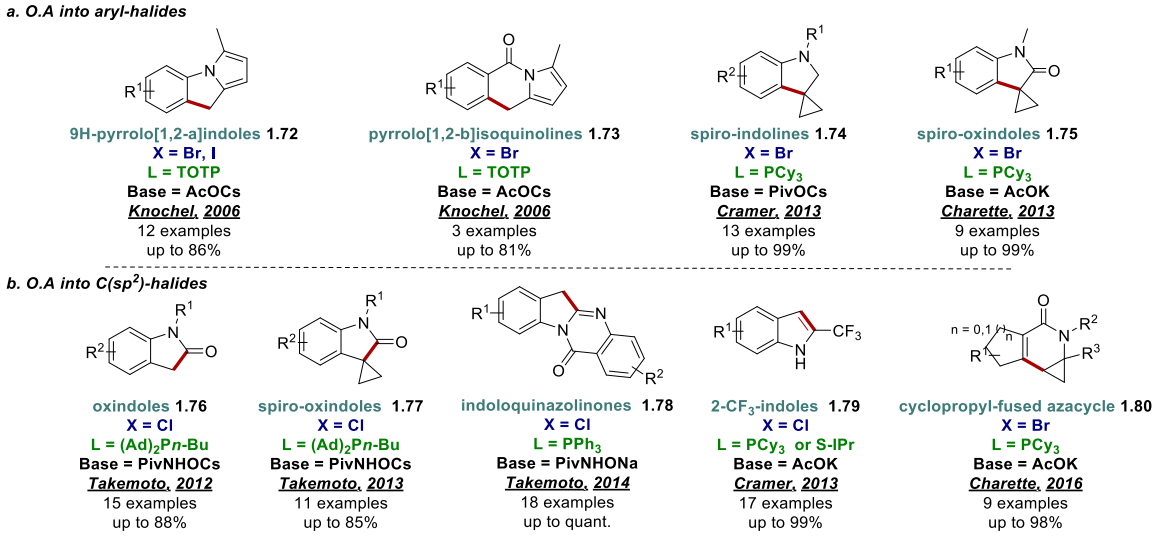
Scheme 16 : *Scope of the Pd(0)-Catalyzed C(sp^3)-H arylation of unactivated C-H bonds*

Fused carbacycles such as indanes **1.61**[32, 33b], indanones **1.64**[33b], indanols **1.69**[42], indanamines **1.70**[42] and fused heterocycles such as dihydrobenzofurans **1.62**[33b], indolines **1.63**[33b, 43], benzolactams **1.65**[44] and benzosultams **1.66**[44] were accessed in high yield and selectivity for

methyl C-H bonds. Interestingly, scarce methylene activation was observed in the synthesis of indolines **1.63**[43]. Attractive tricyclic compounds **1.67**[45] were also built via double C(sp^3)-H activation or starting from bicyclic precursors **1.68**[46]. Selective C(sp^3)-H activation in α to heteroatoms was also observed in the synthesis of benzolactams **1.65**[44] and benzosultams **1.66**[44].

4.2.4. Intramolecular activation of more activated C(sp^3)-H bonds

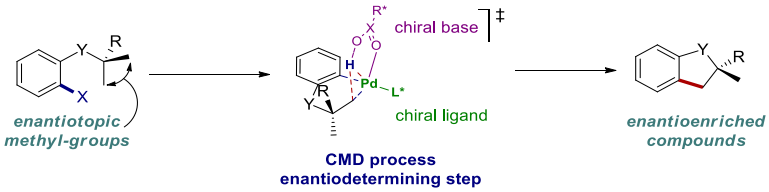
Pd(0)-catalyzed intramolecular activation of more activated C(sp^3)-H bonds was also exploited. Several examples were described and can be subdivided based on the type of oxidative addition involved. Firstly, classical O.A into aryl-halides leads to C(sp^3)-H arylated compounds (Scheme 17 a.). Knochel and coworkers initially took advantage of benzylic positions to yield indoles **1.72** and isoquinolines **1.73** derivatives in high yield[47]. Later, Cramer and Charette developed syntheses of spiroindolines **1.74**[48] and spirooxindoles **1.75**[49] via C(sp^3)-H activation of methine bonds. By contrast, O.A can take place into non-aromatic C(sp^2)-halides bonds as already described in cross-coupling reactions. In 2012, Takemoto and coworkers achieved the synthesis of various oxindoles using the C(sp^3)-H carbamoylation of benzylic bonds **1.76**[50] and have further extended this methodology to methine bonds, thus furnishing a new route to spiro-oxindoles **1.77**[51]. Following this work, the same group reported an efficient synthesis of indoloquinazolinones **1.78** via the activation of chloroquinazolinones[52]. Using the same idea of non-classical oxidative addition, Cramer and coworkers described the synthesis of valuable perfluoroalkylated indoles based on the C(sp^3)-H imidoylation of benzylic C-H bonds **1.79**[53]. Finally, Charette recently reported a method to access cyclopropyl-fused azacycles through C(sp^3)-H alkenylation **1.80**[54] (Scheme 17).



Scheme 17 : *Scope of the Pd(0)-Catalyzed intramolecular C(sp^3)-H arylation of activated C-H bonds*

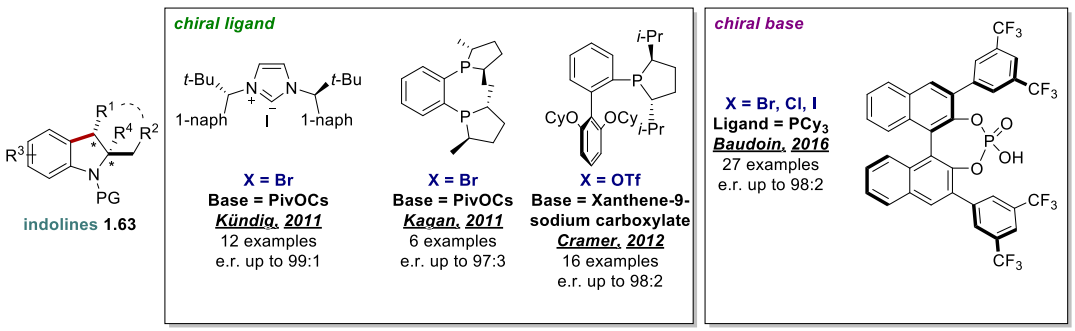
4.2.5. Enantioselective intramolecular C(sp^3)-H bonds activation

In most biological compounds, homochirality is observed inducing high levels of chemical chirality in living systems. This structural complexity often leads to different behaviours among various enantiomers, notably in drug effectiveness (*e.g.* Thalidomide drama). Therefore, development of asymmetric synthesis is of great interest for the pharmaceutical as well as the agrochemical and fragrance industries. In intramolecular C(sp^3)-H bond activation, two main strategies were used to discriminate enantiotopic alkyl groups. Thanks to experimental and computational studies, it is well accepted that the CMD process involving an ancillary ligand and a base is the enantiodetermining step. Taking advantage of a chiral ligand and/or a chiral base, enantioenriched compounds can be obtained (Scheme 18).



Scheme 18 : *Two main strategies for enantioselective C(sp^3)-H activation*

These two strategies were successfully applied to the synthesis of highly enantioenriched (fused)indolines **1.63** which are important scaffolds among natural products and active pharmaceutical ingredients (API) (Scheme 19)[55]. In 2011, Kündig and coworkers reported the first enantioselective Pd(0)-catalyzed C(sp^3)-H activation using C2-symmetric *N*-heterocyclic carbenes (NHCs)[56]. Moving to chiral phosphine ligands, Kagan[57] and Cramer[58] could reach similar enantiomeric ratio. In these latter reports, they interestingly showed that it could be possible to discriminate enantiotopic alkyls groups using chiral bases, however with moderate *e.r.* and reactivity. In 2016, Baudoin and coworkers described the first highly enantioselective Pd(0)-catalyzed C(sp^3)-H activation involving a binol-derived chiral base and an achiral ligand[59] (Scheme 19).



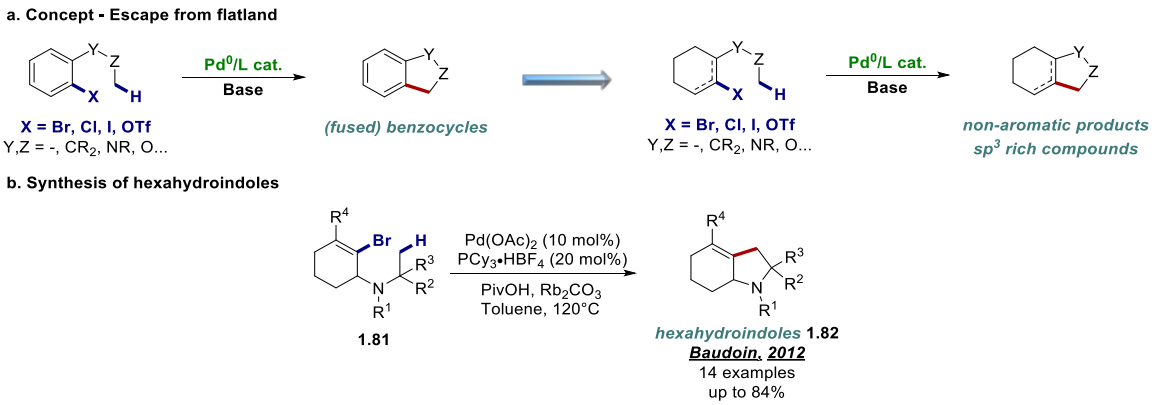
Scheme 19 : *Synthesis of chiral indolines*

Simultaneously to the work based on chiral ligands for the synthesis of enantioenriched indolines, Baudoin reported a highly diastereoselective and moderately enantioselective synthesis of fused cyclopentanes[60] **1.61 (**Scheme 16**)** using binepine-type ligands. Thanks to further improvements on the ligand structure and reaction conditions, high *d.r.* and *e.r.* were achieved, leading to fused cyclopentanes with two or three contiguous stereocenters[61].

On the other hand, applications of the intramolecular activation of more activated C(sp^3)-H bonds in an enantioselective fashion was also explored by Cramer. Using TADDOL-type ligands such as phosporamidites or phosphonites to discriminate benzylic or cyclopropane C-H bonds[62], they provided efficient enantioselective syntheses of chiral tetrahydroquinolines[63], chiral dihydroquinolones and dihydroisoquinolones[64], chiral β-lactams[65] and cyclopropane-fused γ-lactams[66].

4.2.6. Extension to intramolecular C(sp^3)-H alkenylation

Until 2012 and still today, methodologies using C(sp^3)-H activation were mostly restricted to the use of aryl halides or triflates that led, after C-H activation, to fused benzocycles. With this in mind, Baudoin and coworkers hypothesized that it could be possible to move from C-H arylation to C-H alkenylation (Scheme 20 a.). Starting from bromoalkenes, this could lead to interesting sp^3-rich compounds. With the optimal bromoalkene substrate **1.81** in hand, they developed a unique route to hexahydroindole compounds **1.82** by C(sp^3)-H alkenylation (Scheme 20 b.)[67]. More details on this strategy are provided in paragraph 1 of Chapter 2 and paragraph 1.1 of Chapter 3.

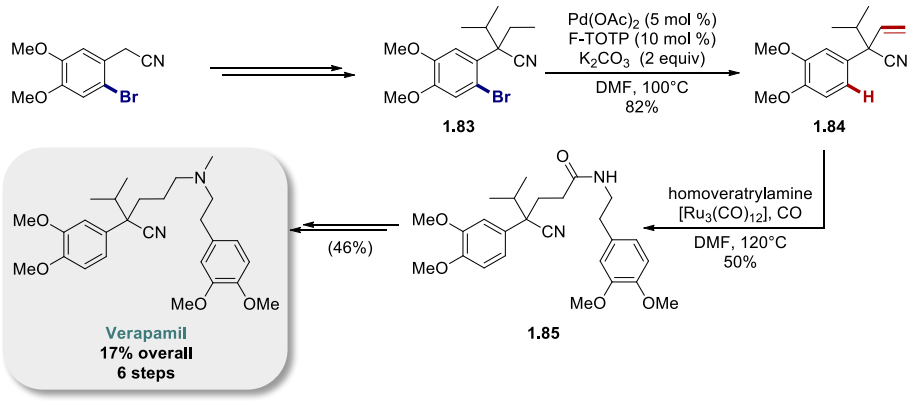


Scheme 20 : *First general Pd(0)-catalyzed intramolecular C(sp^3)-H alkenylation*

4.2.7. Applications of C(sp^3)-H activation to the total synthesis of natural products

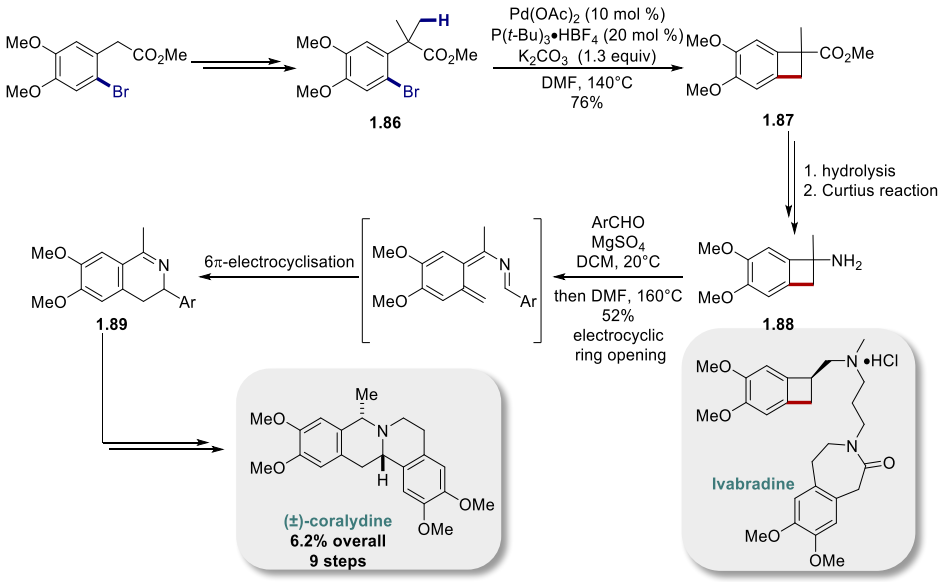
In organic synthesis, the decisive testimony of value is synthetic utility. Despite significant developments, applications of oxidative-addition-initiated activation of unactivated C(sp^3)-H bonds for the total synthesis of natural products or API remain scarce. Nevertheless, the group of Baudoin reported pioneering examples.

In 2007, they achieved the total synthesis of Verapamil, a calcium-channel blocker. Taking advantage of the newly designed F-TOTP phosphine allowing dehydrogenation under milder conditions, they obtained the product **1.84** in high yield and selectivity (ethyl *vs.* *i*-Pr) starting from the readily available compound **1.83**. After optimization of a three-step sequence including notably a ruthenium-catalyzed hydroamidation leading to **1.85**, they successfully obtained Verapamil in good overall yield (*Scheme 21*)[32].



Scheme 21 : *Total synthesis of verapamil*

In 2009, the same research group described a new synthesis of 3,4-dihydroisoquinolines (DHIQ) based on two pivotal C-H activations and pericyclic reactions[68]. Thanks to the previously reported BCB synthesis (Scheme 13), they obtained in high yield the BCB **1.87**, which after hydrolysis followed by a Curtius rearrangement yielded the amine **1.88**. Then, after condensation with the appropriate aldehyde, they triggered, under thermal activation, an electrocyclic ring-opening/6π-electrocyclization furnishing the DHIQ **1.89**. Finally, a three-step sequence allowed the total synthesis of the tetrahydroprotoberberine alkaloid (±)-coralydine in good overall yield (*Scheme 22*). In addition, thanks to a collaboration with Servier, they showed that the synthesis of BCB via C-H activation could be applied to the synthesis of the cardiotonic drug Ivabradine.



Scheme 22 : *Total synthesis of (±)-coralydine*

On the other hand, applications of intramolecular activation of more activated C(sp^3)-H bonds was also developed by Takemoto[69] and Cramer[64].

4.2.8. Research aim and work described in this thesis

In the last decade, the transition metal-catalyzed intramolecular activation of unactivated C-H bonds has emerged as a powerful method to transform otherwise inert entities. Within this field, we recently developed a straightforward access to hexahydroindoles by intramolecular C(sp^3)-H alkenylation starting from bromoalkenes (Scheme 20).

In this thesis, we will first report the use of this intramolecular C(sp^3)-H alkenylation in combination with a directed C(sp^3)-H arylation to achieve a divergent synthesis of aeruginosins.

In a second part, based on this intramolecular C(sp^3)-H alkenylation, we will report the development of a modular C(sp^3)-H alkenylation leading to γ-lactams, which are prevalent scaffolds found in numerous bioactive natural molecules.

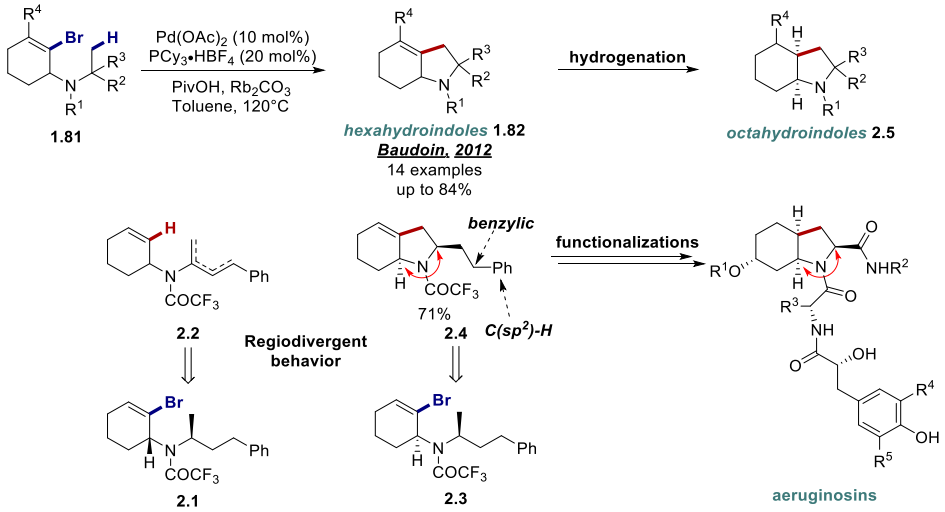
Finally, a highly efficient synthesis of β-lactams by palladium(0)-catalyzed-C(sp^3)-H carbamoylation, will be described. These latter are valuable compounds widely used in pharmaceutical chemistry

Chapter 2

Divergent synthesis of aeruginosins based on a C(sp^3)–H activation strategy

1. Initials work

As mentioned in paragraph 4.2.6 of Chapter 1, Baudoin and coworkers have established a new route to hexahydroindoles based on intramolecular C(sp^3)–H alkenylation[67]. During this study, an interesting diastereodivergent behaviour was observed. Indeed, **2.1** gave an undesired mixture of olefin by-products **2.2** arising from C-H activation followed by β-hydride elimination, whereas **2.3** furnished the desired *cis*-configured cyclized product **2.4** with a remarkable site-selectivity even in the presence of benzylic and C(sp^2)-H bonds. Such regiodivergent behaviour was already observed by Kündig in enantioselective C(sp^3)-H arylation[70] and results mainly from steric/conformational aspects and ligand effect. Interestingly, product **2.4** arising from *syn*-precursor **2.3** provided the desired *cis*-configuration observed in aeruginosins (red arrow). Furthermore, hydrogenation of these indoles **1.82-2.4** allows to obtain *cis*-octahydroindoles **2.5** which are typical moieties that can be found in the aeruginosin marine natural products. We thus envisioned to apply this methodology to the synthesis of this family of natural products (Scheme 23).



Scheme 23 : *Diastereodivergent synthesis of hexahydroindoles – Road to aeruginosins*

2. Aeruginosins marine natural products

2.1. Introduction

In 1994, Murakami and coworkers reported the isolation of aeruginosin 298A from the toxic blue algae *Microcystis aeruginosa*. This was the first compound of a new family of linear peptides[71]. This family currently contains more than sixty different congeners isolated from sponges or cyanobacterial sources[72]. These congeners are structurally close to the structure of aeruginosin 298A depicted in Figure 2, but present some variations such as alteration of the 2-

carboxy-6-hydroxyoctahydroindole (Choi) moiety (dysinosin A), a halogenated hydroxyphenyllactic acid (HPLA) residue (aeruginosin 98A; Scheme 24), an additional carbohydrate moiety (aeruginosin 828A)… Moreover, among those of them which were biologically tested, inhibition against serine proteases, which are involved in the blood coagulation cascade, was observed[73].

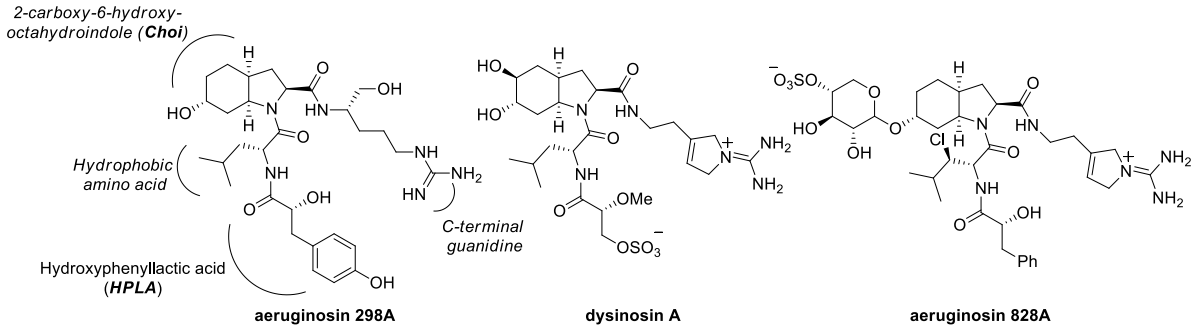


Figure 2 : *Structural variety of aeruginosin congeners*

Since the first isolation by Murakami and full-characterization using X-ray crystallography by Tulinsky[74], numerous groups investigated the total synthesis of these marine natural products. Two main disconnections were established to allow the synthesis of the *L*-Choi core. First, Bonjoch[75] and Wipf[76] described an intramolecular Michael-type addition strategy employing *L*-tyrosine in a reductive or oxidative process to build the C7a-N bond. Notably, completion of the total synthesis of aeruginosins 298A by Bonjoch has permitted a structural revision with re-assignment of the Leu- amide subunit (from *L*- to *D*-Leu). For their part, Shibasaki[77] and coworkers have used a catalytic asymmetric phase-transfer alkylation of a glycine derivative. In all these cases, mixture of diastereoisomers were obtained requiring additional thermodynamic equilibration to obtain reasonable yield of the desired configuration of the Choi unit. In contrast, methodologies used by Trost[78] or Carreira[79] allow a direct access to the required configuration of the octahydroindole. On the other hand, Hanessian and coworkers[80] have developed an aza-Prins bromocarbocyclization which leads to the bicyclic system through the formation of the C7-C7a bond (Figure 3).

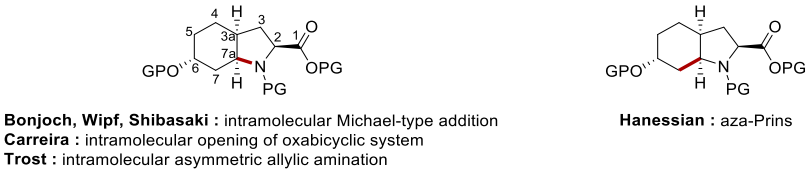
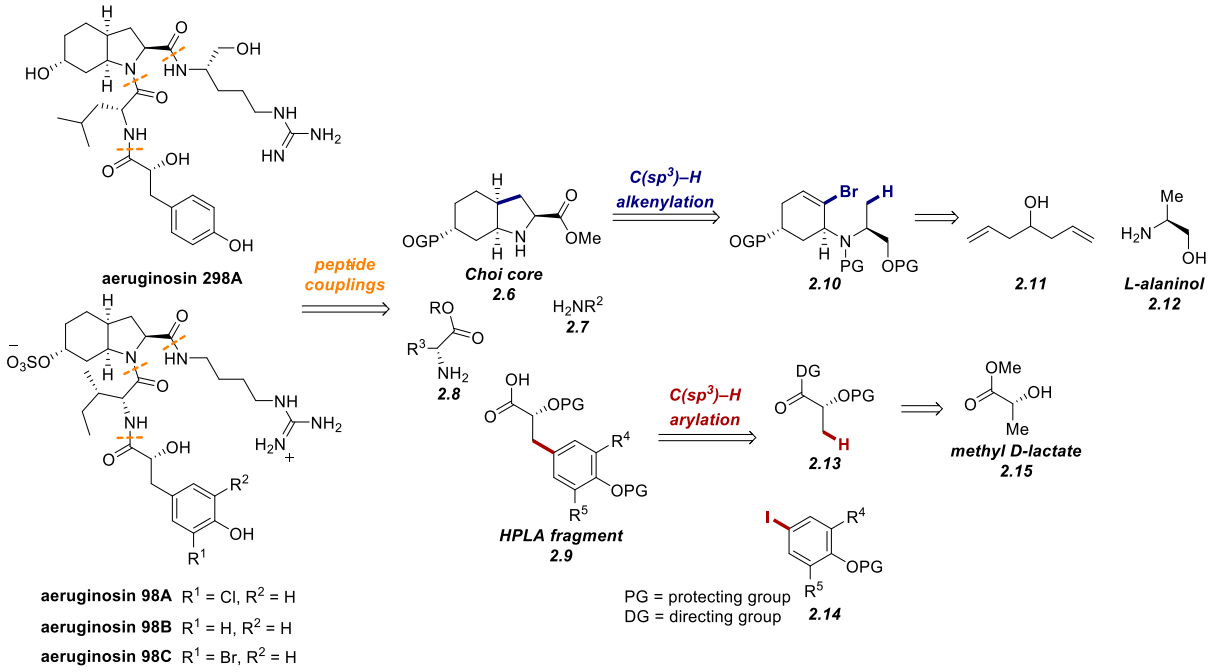


Figure 3 : *Previous disconnections for the synthesis of the L-Choi core*

3. Total synthesis of Aeruginosins 298A, 98A, 98B and 98C.

3.1. Goal of this project and retrosynthetic analysis

The goal of this study was to develop a general approach for the synthesis of various aeruginosins as well as suggesting new disconnections based on methodologies relying on metal-catalyzed C-H activation. The following retrosynthetic plan was considered for the synthesis of these aeruginosins. The use of three classical peptide couplings would give us access to compounds **2.6** to **2.9**. Then, we envisioned to obtain the *L*-Choi core **2.6** in a straightforward and scalable manner through our recently developed intramolecular C(sp^3)-H alkenylation[67] shown previously in (Scheme 23). In addition, an intermolecular C-H arylation starting from **2.13** and **2.14** would lead to the HPLA fragment **2.9** in an efficient manner[81]. Finally, the C-H activation precursors **2.10-2.13** would be easily prepared from the readily available starting materials **2.11-2.12-2.15** (Scheme 24).



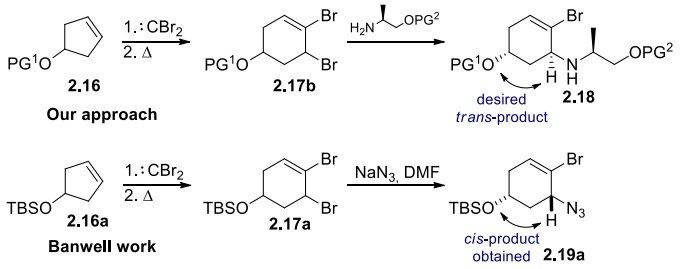
Scheme 24 : *Retrosynthetic analysis*

3.2. Synthesis of the Choi core

3.2.1. Initial mechanistic study

After having considered different ways to obtain the enantiomerically pure precursor of C-H activation **2.10** with the desired *trans*-relationship, we hypothesized that we could take advantage of the intrinsic reactivity of easily accessible gem-dihalocyclopropanes to provide a short and efficient access to **2.10**[82]. Indeed, gem-dihalocyclopropanes are readily available *via*

the mild addition of a dihalocarbene[83] to the corresponding alkenes and are useful building-blocks for the preparation of valuable substituted hydrocarbon systems. Offering new retrosynthetic possibilities, these precursors were widely used in the total synthesis of alkaloids[84]. Notably, such gem-dihalocyclopropane intermediates are prone to electrocyclic ring-opening under thermal or silver-promoted conditions generating the corresponding π-allylic cation, which can be trapped inter- or intramolecularly by various nucleophiles. Starting from the protected cyclopent-3-enol **2.16**, we envisioned a three-step sequence involving dibromocyclopropanation followed by electrocyclic ring-opening and nucleophilic substitution to reach in an efficient manner the desired *trans*-product **2.18** despite possible diastereoselectivity issues. Indeed, Banwell and coworkers, during their total synthesis of the crimine alkaloid hamayne, have reported the *cis*-diastereoselective synthesis of the product **2.19a** using a similar sequence with nucleophilic substitution with sodium azide[85]. Starting from a 6:1 diastereoisomeric ratio of **2.17a**, they have obtained product **2.19a** with a diastereoselectivity of 9:1, thereby indicating a S_N1-type mechanism. Interestingly, this *cis*-configuration was not expected considering the steric hindrance of the TBS-group, thereby that the stereoselectivity of this reaction is controlled by stereoelectronic effects. Nevertheless, we surmised that stereoselectivity could be mainly controlled by steric effects when using a bulkier alaninol-derived nucleophile and hydroxy-protecting group (Scheme 25).

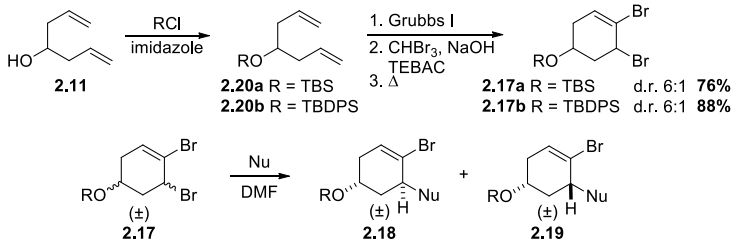


Scheme 25 : *Synthetic plan of precursor*

In order to test our hypothesis, we studied both the influence of the nucleophile and of the protecting group on the diastereoselectivity. Thanks to a four-step sequence, we have efficiently prepared two racemic silyl-protected dibromocyclohexenols **2.17a-2.17b** with a diastereoisomeric ratio of 6:1. To conduct this study, we submitted dibromocyclohexenols **2.17a-2.17b** to nucleophilic substitution with azide and primary amines. First, in contrast to the *cis*-selectivity observed with azide as nucleophile (entry 1), primary amines (entries 2-4) led to an inversion of diastereoselectivity in favour of the *trans* product **2.18**. Interestingly, even the use of the non-sterically demanding *N*-propyl amine resulted in significant inversion (entry 2), thereby supporting a stereoselective control by stereoelectronic and steric effects.

Indeed, more-hindered α-substituted amines increased significantly the diastereoselectivity (entries 2-4 and 6-8). Moreover, high influence of the silyl protecting group was observed for each considered nucleophile. Particularly, the bulkier TBDPS group of **2.17b** has considerable impact (two-fold higher) compared to the TBS group of **2.17a** on the diastereomeric ratio for both *cis* and *trans* isomers **2.18-2.19** (entries 5-8 *vs.* 1-4). This preliminary study allowed us to access both *cis* and *trans* diastereoisomers of 5-aminocyclohex-3-en-1-ols in high *d.r.* depending on the nucleophiles and protecting groups used. Nevertheless, it could be interesting to try various other nucleophiles to get a better understanding of the factors controlling these opposite selectivities (*Table 1*).

Table 1 : *Study of the allylic nucleophilic substitution*



Entry	R	Nucleophile (Nu)	d.r.[b]
1	TBS	N_3^-	1 : 8
2		*n*-PrNH$_2$[c]	3 : 1
3		*i*-BuNH$_2$[c]	3 : 1
4		*i*-PrNH$_2$[c]	6 : 1
5	TBDPS	N_3^-	1 : 15
6		*n*-PrNH$_2$[c]	7 : 1
7		*i*-BuNH$_2$[c]	8 : 1
8		*i*-PrNH$_2$[c]	11 : 1

[a]TBDPS = tert-butyldiphenylsilyl; TEBAC = Et_3BnNCl. [b] Ratio of **2.18**:**2.19** determined by 1H NMR of the crude reaction mixture. Relative configurations of the major diastereoisomers obtained with sodium azide and isopropylamine were determined by X-ray analysis of ferrocene derivatives **2.21-2.21'** (Figure 4). For other primary amines, the trans configuration was ascribed to major diastereoisomers by analogy of their chemical shifts in 1H NMR. c In combination with 1.1 equiv. K_2CO_3.

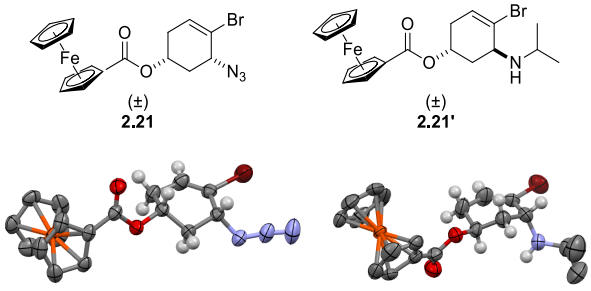
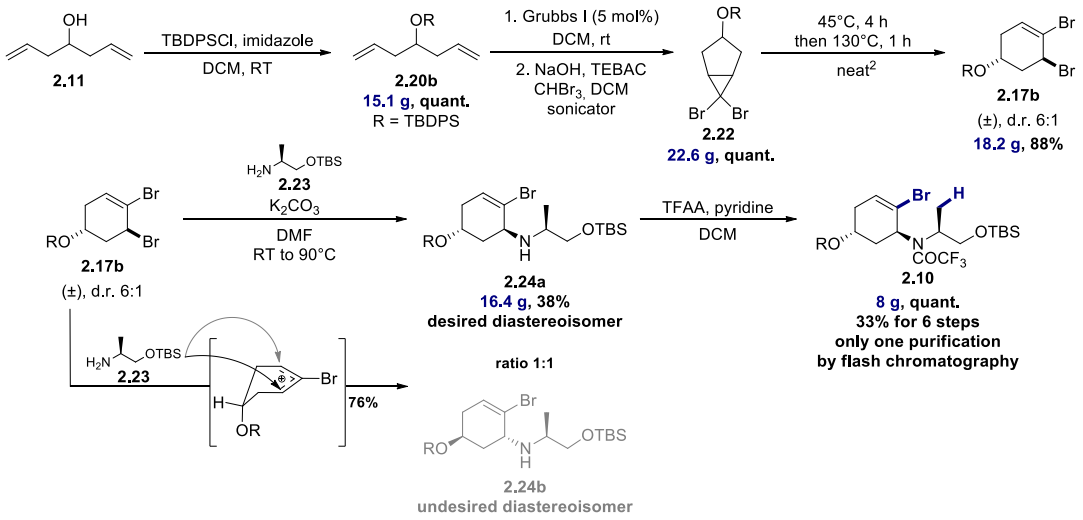


Figure 4 : *X-ray structures of major diastereoisomers*

3.2.2. Scale-up synthesis of the precursors of C(sp^3)-H activation

Starting from 1,6-heptane-dien-3-ol **2.11**, we have conducted the protection of the hydroxy function with the bulky TBDPS silyl group followed by olefin metathesis to afford **2.16** in quantitative yield. Of note, the use of Grubbs I catalyst at room temperature proved to be crucial to avoid polymerized by-products. Under modified Makosza's conditions[83], gem-dibromocyclopropane **2.22** was obtained quantitatively in an undetermined mixture of *trans*/*cis* products due to complicated NMR interpretation. Taking advantage of work reported by Fleming and Thomas[86], where they described that the reaction proceeded via a stereospecific rearrangement of the gem-dichlorocyclopropane to the allyl chloride, we assume that the *trans:cis* ratio of **2.22** should be close to 6:1 (in favor of the *trans* isomer*)* due to the ratio for compound **2.17b**. This latter was obtained by the thermal electrocylic ring-opening of **2.22**, as an inconsequential 6:1 mixture of diastereoisomers in high yield. Subsequent nucleophilic substitution of TBS-protected *L*-alanilol **2.23** with dibromocyclohexenol **2.17b** furnished a 1:1 mixture of two diastereoisomers **2.24a-2.24b** both possessing the required *trans* relationship at the cyclohexene ring. This outcome can be explained by the formation of the expected symmetrical allyl cation arising from the S_N1-type mechanism, which can be attacked by the nucleophile **2.23** unselectively on both electrophilic positions, opposite to the sterically-demanding OTBDPS group. Gratifyingly, desired diastereoisomer **2.24a** was easily isolated by flash column chromatography and protected as a trifluoroacetamide. At this stage, intermolecular asymmetric allylic alkylation was also tried using classical conditions and chiral ligands, introduced by Trost and coworkers[87], to obtain **2.24a** in enantiomerically pure form starting from **2.17b** and derivatives, without success (Scheme 26).



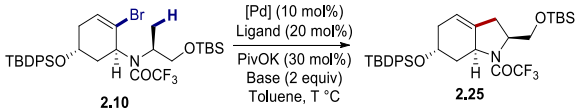
Scheme 26 : *Multi-gram scale synthesis of precursor of C(sp^3)-H activation*

Despite the loss of 50% of the material through the production of the undesired diastereoisomer **2.24b**, this synthetic strategy has proved to be highly efficient allowing the production of 8g of bromocyclohexene **2.10** in 33% overall yield over 6 steps (83% average yield per step).

3.2.3. Palladium-catalyzed intramolecular C(sp^3)-H activation

Then, we investigated the key intramolecular C(sp^3)-H alkenylation step. Using previously reported conditions as starting point, we were pleased to find that the desired product **2.25** was obtained in 45% yield with concomitant debrominated and mixture of olefin by-products (entry 1). Thanks to palladium sources and ligands screening, we established that a combination of the well-defined palladium complex ($Pd(PCy_3)_2$) with potassium pivalate as active base in toluene at 120°C furnished the bicyclic system **2.25** with good yield (*Table 2*).

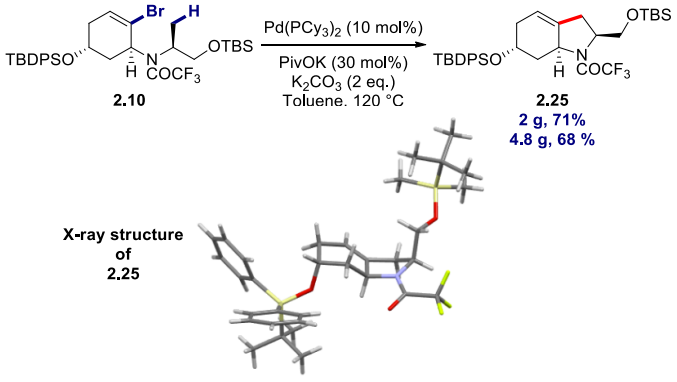
Table 2 : *Selected conditions of the optimization*



Entry	[Pd]	Ligand	Base	T °C	Yield %[a]
1	$Pd(OAc)_2$	PCy_3•HBF_4	Rb_2CO_3	120	45
3	Pd_2dba_3	PCy_3•HBF_4	Rb_2CO_3	120	45
2	$Pd(PPh_3)_4$	–	Rb_2CO_3	120	32
4	$Pd(PCy_3)_2$	–	Rb_2CO_3	120	75
5	$Pd(PCy_3)_2$	–	Rb_2CO_3	110	70
6	$Pd(PCy_3)_2$	–	Rb_2CO_3	100	18
7	$Pd(PCy_3)_2$	–	Cs_2CO_3	120	40
8	$Pd(PCy_3)_2$	–	K_2CO_3	120	85
9[b]	$Pd(PCy_3)_2$	–	K_2CO_3	120	50

[a] NMR yield, determined by ^1H NMR using trichloroethylene as an internal standard. [b] Using 5 mol% of $Pd(PCy_3)_2$.

Then, we gradually scaled up the reaction allowing the preparation of almost 5g of the hexahydroindole moiety in a reproducible manner. Furthermore, the absolute configuration of the bicyclic product was confirmed by NMR and X-ray analysis (Scheme 27).

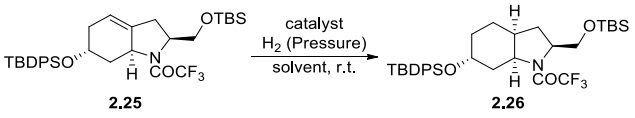


Scheme 27 : *Scale-up of the C(sp^3)-H alkenylation*

3.2.4. Hydrogenation of the hexahydroindole system

With the hexahydroindole compound **2.25** in our hand, we studied the reduction of the trisubstituted alkene to access the octahydroindole moiety **2.26** using either homogeneous or heterogeneous catalysis. First, both the homogeneous Wilkinson's catalyst and the more reactive cationic Crabtree's catalyst were totally inefficient (entries 1-2). We next turned our attention to heterogenous catalysts such as Adam's or Pearlman's catalyst which already proved to be efficient on simplified hexahydroindole scaffolds (entries 3-4)[67]. Unfortunately, no conversion was observed on the more advanced intermediate **2.25**. Finally, we were pleased to find complete reactivity with rhodium on activated charcoal. Interestingly, diastereoselectivity of the reduction of this trisubstituted alkene was affected by the hydrogen pressure. Gratifyingly, this latter was maximal with one atmosphere of hydrogen (entry 7), whereas a decreased *d.r.* was observed when a higher pressure was applied (entry 8-10). Importantly, the complete diastereocontrol of the reduction was observed on the convex face (induced by the angular carbon) of the hexahydroindole **2.25**. The desired *cis*-configuration was confirmed by 2D-NOESY NMR and by X-ray analysis (*Table 3*).

Table 3 :** Optimization of the hydrogenation of **2.25



2.25 **2.26**

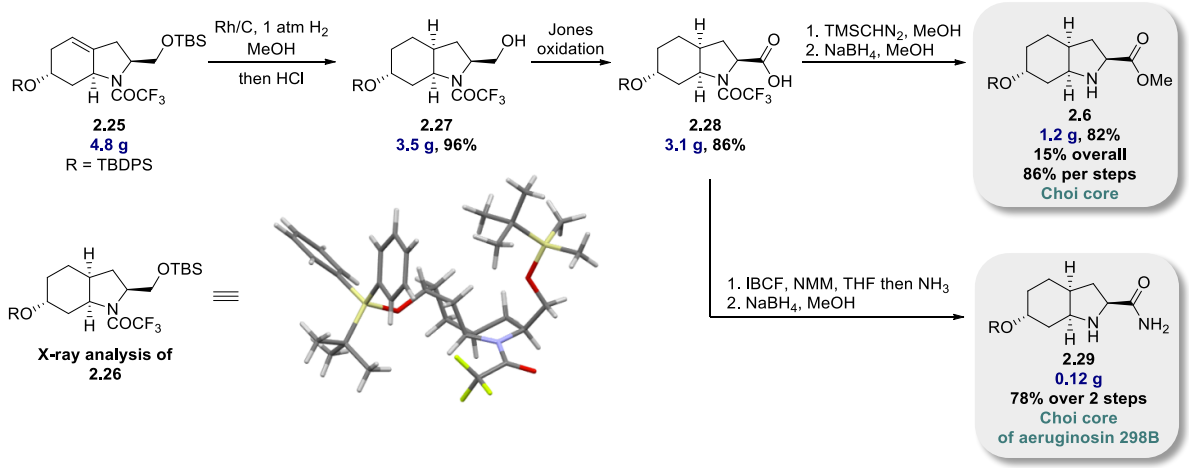
Entry	catalyst	solvent	P_{H_2} (bar)	Conv. (%) [a]	d.r. [a]
1	$RhCl(PPh_3)_3$	EtOAc	1	–	–
2	$[Ir(COD)(C_5H_5N)(PCy_3)]PF_6$	EtOAc	1	–	–
3	$Pd(OH)_2/C$	THF	1	–	–
4	PtO_2	MeOH	1	< 10	–
5	Ru/Al_2O_3	EtOAc	1	< 10	–
6	Ru/C	EtOAc	1	< 10	–
7	Rh/C	EtOAc	1	100	>20:1
8	Rh/C	EtOAc	3	100	10:1
9	Rh/C	EtOAc	10	100	8:1
10	Rh/C	EtOAc	20	100	6:1

[a] *NMR yield, determined by ^1H NMR using trichloroethylene as an internal standard.*

3.2.5. Completion of the synthesis of the Choi core

During the scale-up of the hydrogenation reaction furnishing the octahydroindole **2.26** concomitant removal of the TBS group was observed. This could be imputed to residual acidity of the rhodium catalyst. We thus thought to carry out a one-pot sequential hydrogenation/selective deprotection of the primary silyl group under acidic conditions. After optimization, we found out that 0.5% HCl in MeOH allowed to obtain **2.27** in almost quantitative yield over two steps. Finally, after optimization of a three-step sequence involving Jones oxidation (using freshly prepared Jones reagent), esterification using a diazomethane

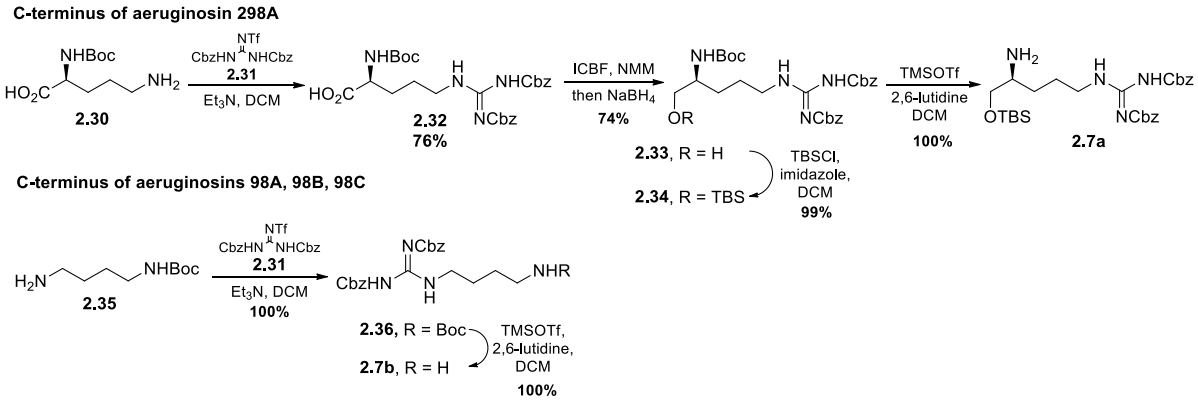
equivalent and reductive cleavage of the *N*-trifluoroacetyl group allowed us to obtain more than 1 g of the amino-ester **2.6** in good overall yield. Moreover, thanks to a two-steps sequence involving mixed carbonic anhydride approach to activate the carboxylic acid, which then reacts with ammonia before a reductive cleavage, we obtained the Choi core **2.29** relevant to the total synthesis of the aeruginosin 298B (Scheme 28).



Scheme 28 : *Synthesis of Choi cores* ***2.6*** *and* ***2.29***

3.3. Synthesis of the C-termini

We first turned our attention to **2.7a**, which is relevant to the synthesis of aeruginosin 298A. Starting from the commercially available *tert*-butoxycarbonyl (Boc)-protected *L*-ornithine **2.30**, we have prepared protected *L*-arginine **2.32** using diprotected triflylguanidine reagent[88] **2.31** under basic conditions. The residual carboxylic acid was reduced under mild conditions[89] using the mixed carbonic anhydride approach avoiding undesired deprotection of Boc or Cbz groups (***Scheme 29***).



Scheme 29 : Synthesis of C-termini

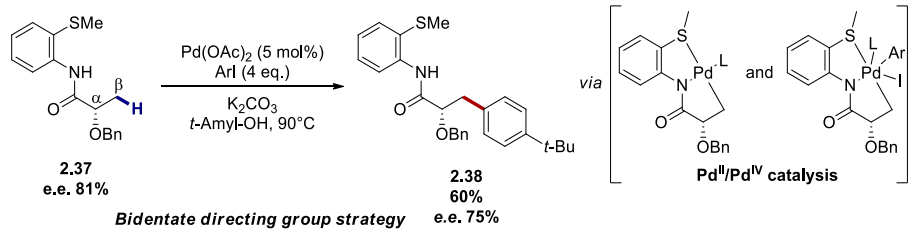
Then, a two-steps sequence involving TBS protection of the primary alcohol **2.33** under classical conditions and Boc deprotection in the presence of TMSOTf allowed to obtain the

L-argol fragment **2.7a** in good overall yield (56% over 4 steps). In parallel, protected *L*-agmatine fragment **2.7b** was yielded using the two-step sequence previously described by Trost and coworkers[78].

3.4. Synthesis of the HPLA fragment and south part

In parallel to the synthesis of the Choi core and C-termini fragments, we envisioned the synthesis of the HPLA fragment via direct C-H activation. In 2005, Daugulis and coworkers established a new approach to yield β- and γ-arylation of unactivated C(sp^3)-H bonds, thanks to bidentate coordinating groups such as 8-aminoquinoline and picolinamide which allow to obtain a high level of regioselectivity and high reactivity due to precoordination to the metal center.[81a, 81c]. Based on Pd^{II}/Pd^{IV} catalysis[90], this pioneering work served as an inspiration for numerous developments of bidentate directing groups[91], methodologies[92] and applications in total synthesis of natural products and API[93].

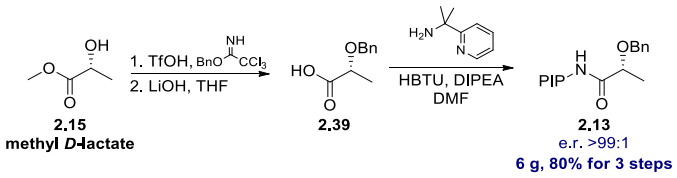
In this regard, we first considered Daugulis' only example of Beta-arylation of lactic acid derivative **2.37** using 2-methylthioaniline as a directing group[81b]. However, under these conditions, an undesired loss of optical purity was observed (**2.38)**. Consequently, we further optimize this transformation in order to reduce the erosion of this sensitive stereogenic center (Scheme 30).



Scheme 30 : *Initial result on lactic acid derivative*

At the outset of our study, only directing groups based on 8-aminoquinoline[81c], 2-methylthioaniline[81b] and 2-pyridinylisopropyl (PIP)[94], introduced by Bing-Feng Shi, proved suitable to obtain β-arylation of unactivated C(sp^3)-H bonds. To design our protecting group strategy, we have first considered previous total syntheses of aeruginosins as well as the directed arylation of the lactate moiety. In agreement with these considerations, benzyl group was chosen for the lactate moiety whereas triisopropylsilyl ether (TIPS) was selected for the phenol derivatives. Of note, selective monoarylation is known to be sometimes complicated to control via directed C-H arylation notably due to the formation of hardly separable polyarylated by-products. These different directing groups were tested under some selected conditions, and PIP group was selected because this latter allowed the transformation without racemization and

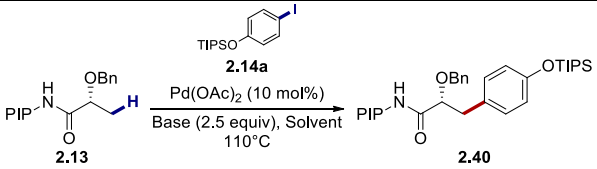
with the highest monoarylation yield. We then turned our attention to the optimization of both the synthesis of the precursor **2.13** and its following intermolecular C(sp^3)-H arylation. Starting from readily available methyl D-lactate **2.15**, a three-step sequence allowed the multigram synthesis of **2.13** in high overall yield (Scheme 31).



Scheme 31 : *Synthesis of C-H arylation precursor **2.13***

After screening of various parameters such as base, equivalents of aryl iodide **2.14a**, solvent, temperature, concentration as well as catalyst loading, we identified potassium carbonate and acetronitrile as optimal base and solvent to maintain a good ratio between **2.40a** and **2.13**. Importantly, four equivalents of aryl iodide **2.14a** were required to achieve acceptable yield of β-arylated product **2.40a** (*Table 4*).

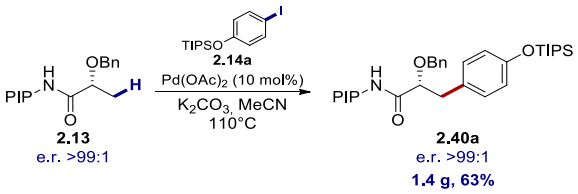
Table 4 : *Selected conditions for optimization of the intermolecular arylation*



Entry	[Pd] (mol %)	ArI (equiv)	Base	Solvent	Temp.	Yield % 2.40a/2.13[a]
1	$Pd(OAc)_2$ (10)	2	K_2CO_3	*t*-amylOH	110°C	50/10
2	$Pd(OAc)_2$ (10)	2	K_2CO_3	DMF	110°C	0/67
3	$Pd(OAc)_2$ (10)	2	K_2CO_3	Toluene	110°C	12/66
4	$Pd(OAc)_2$ (10)	2	K_2CO_3	Dioxane	110°C	20/60
5	$Pd(OAc)_2$ (10)	2	K_2CO_3	MeCN	110°C	42/45
6	$Pd(OAc)_2$ (10)	4	K_2CO_3	MeCN	110°C	65/7
7	$Pd(OAc)_2$ (20)	4	K_2CO_3	MeCN	110°C	60/15
8	$Pd(OAc)_2$ (10)	4	K_2CO_3	MeCN	90°C	50/30
9	$Pd(OAc)_2$ (10)	4	K_2CO_3	MeCN	130°C	32/30
10	$Pd(OAc)_2$ (10)	4	Na_2CO_3	MeCN	110°C	3/75
11	$Pd(OAc)_2$ (10)	4	Rb_2CO_3	MeCN	110°C	35/41
12	$Pd(OAc)_2$ (10)	4	Cs_2CO_3	MeCN	110°C	0/90
13	$Pd(OAc)_2$ (10)	4	K_3PO_4	MeCN	110°C	58/20

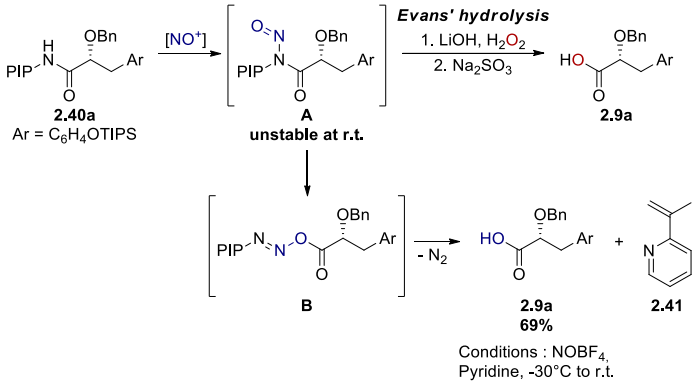
[a] *NMR yield, determined by ^1H NMR using trichloroethylene as an internal standard.*

With the optimal conditions in our hands, we gradually scaled up the reaction allowing the preparation of 1.4 g of **2.40a** in a reproducible manner. Furthermore, no erosion of the enantiomeric excess was observed (Scheme 32).



Scheme 32 : *Scale-up of the C(sp^3)-H arylation*

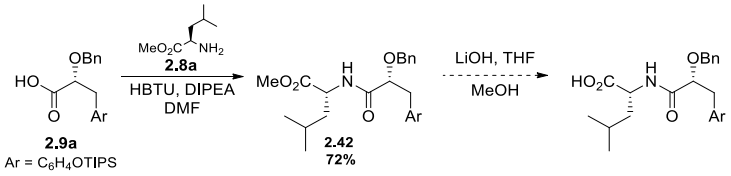
While directing groups allow highly regioselective transformations due to metal precoordination, they also have some drawbacks. For instance, the directing group has to be pre-installated and this latter remains into the products. Consequently, we turned our attention to the removal of the PIP directing group from compound **2.40a**. Cleavage of this latter was not so trivial. Several known conditions such as acidic cleavage, various amide activation followed by Evans' hydrolysis[95], as well as the three-step sequence used by Shi and coworkers[94], involving initial nitrosation with $NaNO_2$/AcOH/Ac_2O failed to give the desired carboxylic acid. Only starting material was recovered in this case. Nevertheless, we tried to improve this initial nitrosation using more reactive NO^+ sources such as *t*-BuONO and $NOBF_4$. Unlike all others reactants, $NOBF_4$ provided consumption of the starting material **2.40a**. We considered literature elements using $NOBF_4$ and were pleased to find that *N*-nitroamide intermediates were unstable and prompt to rearrangement[96]. A lot of efforts were devoted to optimize this process. Notably, the temperature, the amount of pyridine as well as the concentration were found to be critical to obtain a high yield. Gratifyingly, using 10 equiv. of $NOBF_4$ in pyridine at -30°C, the PIP directing group could be cleaved under new and mild conditions for this deprotection relying on the rearrangement of the *N*-nitrosamide **A** into the diazoester **B** to provide the desired carboxylic acid **2.9a** and propenyl pyridine **2.41 (**Scheme 33**)**.



Scheme 33 : *Development of new cleavage conditions for the PIP directing group*

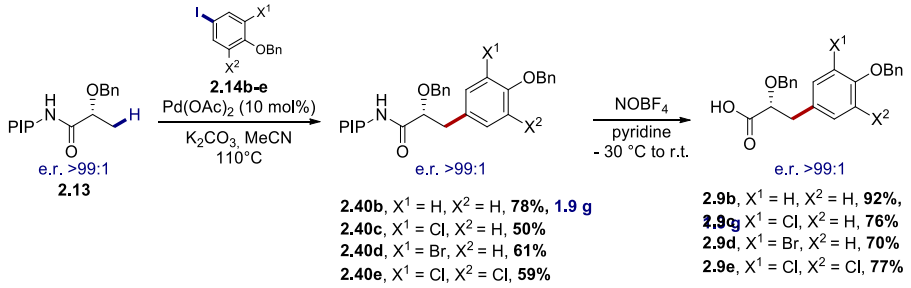
With the required carboxylic acid **2.9a**, we carried on the synthesis of the south-part of aeruginosins 298A using a classical peptidic coupling with *D*-leucine methyl ester **2.8a** to obtain

2.42. Unfortunately, the following hydrolysis led to concomitant and undesired cleavage of the TIPS protecting group (Scheme 34).



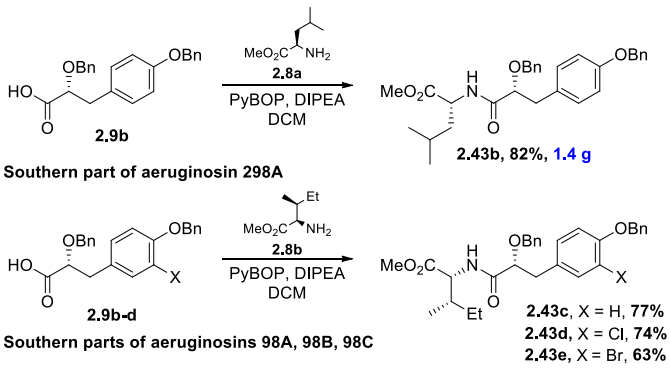
Scheme 34 : *Attempt to synthesize the southern part of aeruginosin 298A*

As a consequence, we focused our attention on protecting groups insensitive to saponification conditions and have chosen benzyl group which can be deprotected during the final hydrogenolysis. Gratifyingly, the two-step sequence involving the directed C-H arylation and the PIP deprotection was more efficient with this benzyl group and more than 1 gram of β-arylated product **2.9b** could be prepared without any loss in the optical purity. This higher overall yield can be explained by a partial degradation of the TIPS group under the reaction conditions employed. Moreover, halogenated HPLA fragments relevant to the total synthesis of aeruginosins 98A, 98C and 101 were synthetized in good overall yield using this versatile strategy (Scheme 35).



Scheme 35 : *New route to HPLA fragment synthesis*

At last, with the required HPLA fragments in our hands, each southern part was accessed using classical peptide coupling with the appropriate amino ester (Scheme 36).

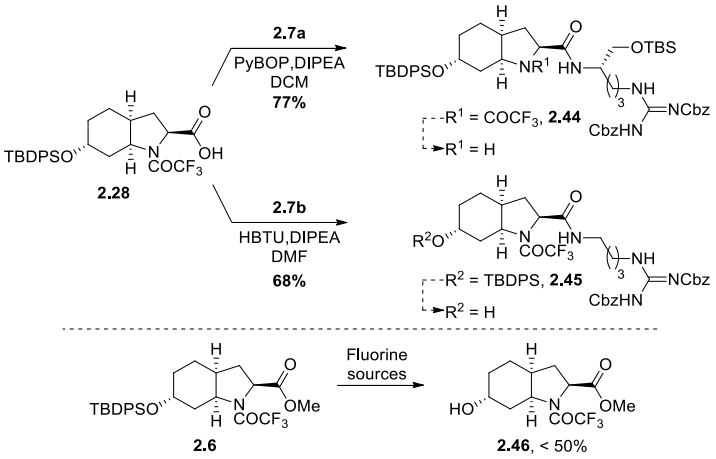


Scheme 36 : *Synthesis of southern parts of aeruginosins*

3.5. Fragment coupling and completion of the total synthesis

3.5.1. First strategies employed

Our first strategy to complete these total syntheses consisted in coupling the Choi core with the C-termini fragments. In both cases, peptide couplings allowed to obtain in acceptable yield **2.44** and **2.45** relevant to the total synthesis of aeruginosins 298A and 98B. We then tried to cleave the *N*-trifluoroacetyl group of **2.44**. While solvolysis conditions (K_2CO_3/MeOH and NH_3/MeOH) led to no conversion, reductive cleavage using sodium borohydride in methanol provided degradation of the guanidine moiety. In parallel, the deprotection of the TBDPS was also investigated. Unfortunately, various conditions using fluorides or acid conditions furnished a mixture of degradation by-products and starting material. On the other hand, removal of the TBDPS group of **2.6** before coupling the C-termini part or southern part proved to be problematic. Due to degradation, only moderate yield of **2.46** was observed by ^{1}H NMR analysis. Thanks to these experiments, we have been able to deduce the most appropriate synthetic sequence for the completion of these total syntheses. Both the *N*-trifluoroacetyl and the TBDPS groups should be cleaved before the installation of the C-termini parts due to the sensitive guanidine fragment. This means that the southern part should be coupled first (Scheme 37).

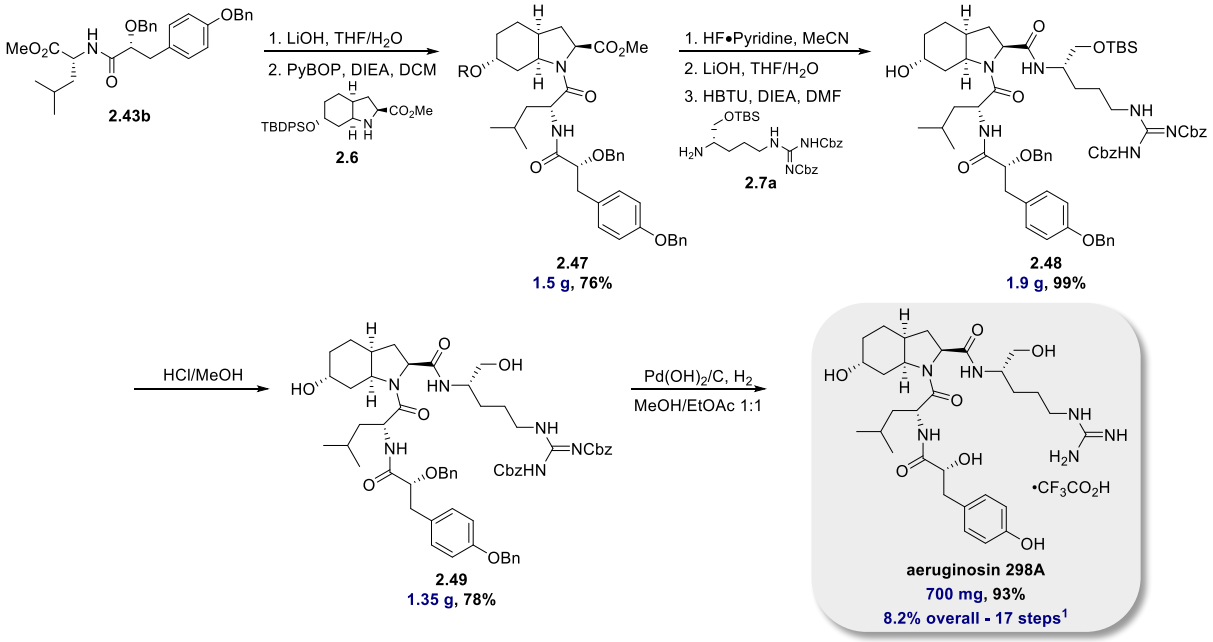


Scheme 37 : *First attempts for deprotection and coupling strategy*

3.5.1. Completion of total synthesis

In accordance with the new roadmap, we first focused our attention to the total synthesis of aeruginosin 298A. Hydrolysis of **2.43b** followed by peptidic coupling with the Choi core **2.6** afforded 1.5 g of **2.47** as a mixture of two rotamers (trans:cis 85:15). This was confirmed by 2D NMR experiments and was in agreement with previously reported analytical data.

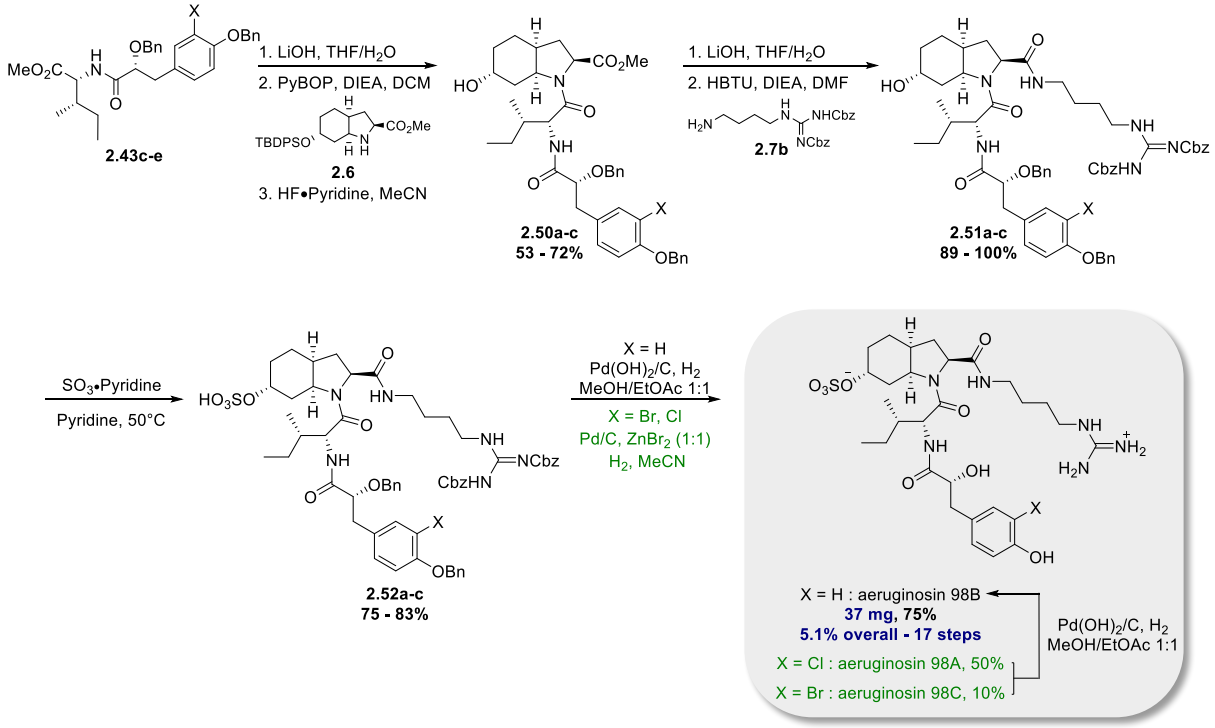
Then, deprotection of the TBDPS protecting group followed by peptidic coupling with the L-argol fragment provided almost 2 g of intermediate **2.48** in almost quantitative yield. Interestingly, in contrast to the previously mentioned deprotection issue, the corresponding free-alcohol was obtained in quantitative yield using Olah's reagent (HF·pyridine**).** Finally, a two-steps sequence involving the acid-mediated cleavage of the residual TBS group followed by classical hydrogenolysis and treatment with trifluoroacetic acid furnished aeruginosin 298 as a salt. Importantly, a 1:1 solvent mixture of MeOH and EtOAc was required during the hydrogenolysis to provide full conversion. This could be explained by solubility issues of the starting material and of partially deprotected intermediates. Of note, 0.7g of aeruginosin 298A was obtained in 8.2% overall yield (86% yield per step) over 17 steps (longest linear sequence), which are both unprecedented in terms of overall yield and scale[97] (Scheme 38).



Scheme 38 : *Total synthesis of aeruginosin 298A*

Taking advantage of this accomplishment, we applied the same strategy to reach the intermediates **2.51a-c** in high overall yield. The resulting free alcohol group was sulphated using conditions previously described by Trost and coworkers[78] (SO_3·pyridine complex) furnishing intermediates **2.52a-c** in good yield. Thanks to hydrogenolysis used as above for **2.49**, total synthesis of aeruginosin 98B was completed in acceptable overall yield. Unfortunately, in the case of aeruginosin 98A and C, total concomitant dehalogenation was observed starting from **2.52b-c** under the same conditions, thus leading to aeruginosin 98B. Such by-reactions are recurrent in total synthesis of naturals products or API due to sensitivity of carbon-halogen bonds.

This issue can be overcome in some specific cases through an internal poisoning of the catalyst by the substrate[98] or by using halides salts to suppress this overreduction[99]. Unfortunately, generalization of these processes is often inefficient and substrate-dependent. Albeit, more than four thousand halogenated natural products were isolated and they often present halogen-dependant bioactivity[100] such as the antibiotic activity of the well-known vancomycin which depends on its chlorine substituents which control the atropisomeric distribution[101]. Gademann and coworkers also observed a halogen-dependant bioactivity for aeruginosin chlorosulfopeptides[102]. Recently, Wu and coworkers have developed a new chemoselective ZnX_2-modulated palladium- or platinum/C catalyst for the hydrogenolysis and hydrogenation of halogen-substituted nitroarenes, alkenes, benzyl ethers as well as aromatic ketones[103]. This methodology does not seem to suffer from any substrates-dependence. Moreover, it is a simple process readily applicable for industrial and academic chemists. Gratifyingly, after optimization of Wu's conditions with model substrates, the use of a 1:1 mixture of palladium on charcoal and zinc bromide in acetonitrile, prevented dehydrohalogenation and allowed the first total synthesis of aeruginosins 98A and 98C[104]. No dehalogenation occurred in the case of the aeruginosin 98A whereas a 1:1 ratio of aeruginosin 98C and aeruginosin 98B was observed, in the case of the brominated precursor **2.52c** (*Scheme 39*).



Scheme 39 : *Total syntheses of aeruginosins 98A, 98B, and 98C*

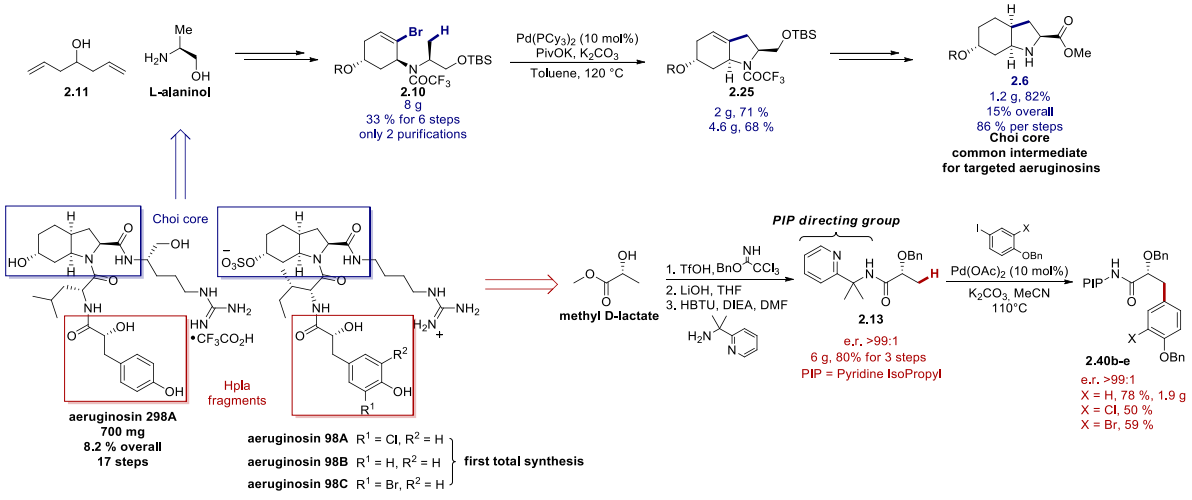
4. Conclusion

Taking advantages of two recently reported C(sp^3)-H bonds activation reactions, we have elaborated a new synthetic route to access aeruginosin marine natural products which exhibit biological activities.

First, we turned our attention to the synthesis of the Choi core. After optimization of the synthesis of the precursor of C-H activation, we were able to apply our recently developed intramolecular C(sp^3)-H alkenylation conditions for the large-scale synthesis of the Choi core which is common to numerous aeruginosins.

On the other hand, a new synthetic approach, using an intermolecular C(sp^3)-H activation, was used to obtain the HPLA fragment of different aeruginosins, highlighting the synthetic versatility of this methodology. It could be interesting to further extend the scope of this methodology to obtain unconventional HPLA fragments or other functionalities, which after completion of the synthesis, would lead to a library of aeruginosins analogues.

Finally, with all the fragments in our hands and thanks to the optimization of the end-game including fine-tuning of the hydrogenolysis step, we have achieved the total synthesis of four aeruginosins including the first total synthesis of halogenated aeruginosins 98A and 98C. Of note, we were able to scale-up the synthesis of aeruginosin 298A to obtain this latter with an unprecedent yield and scale (Scheme 40).



Scheme 40 : *Overview of the total syntheses of aeruginosins 298A, 98A, 98B and 98C*

Chapter 3

Synthesis of Strained γ-Lactams

by Palladium(0)-Catalyzed C(sp^3) Alkenylation

and

Application to Alkaloid Synthesis

1. Introduction

1.1. Historical development of intramolecular C(sp^3)-H alkenylation

As mentioned in paragraph 4.2.6 of Chapter 1, methodologies using C(sp^3)-H activation were mostly restricted to the use of aryl halides or triflates that led, after C-H activation, to fused benzocycles. Until 2012, as for intramolecular C(sp^3)-H arylation, no straightforward methodology using intramolecular C(sp^3)-H alkenylation was developed. This disinterest may be explained by the fact that the corresponding substrates are less readily accessible than the aromatic ones and often require multistep syntheses. Moreover, compared to intramolecular C(sp^3)-H arylation, by-reactions are more prone to occur due to the presence of adjacent aliphatic protons, to insaturation and additional conformational aspects. Nevertheless, our group envisioned to explore such α,β or β,γ vinyl halides as precursors of C-H activation paving the way for the synthesis of new sp^3-rich scaffolds, reactivity studies as well as new disconnections in target-oriented total synthesis (Scheme 41).

Scheme 41 : Formation of sp^3-rich scaffolds by intramolecular C(sp^3)-H alkenylation

Initial work on this topic in our group was reported by Dr. Alice Renaudat in her Ph.D. thesis. By analogy to benzocyclobutenes[33a], our group hypothesized that cyclobutenes and cyclobutanes could be obtained through C(sp^3)-H alkenylation. Often obtained by [2+2] cycloaddition, electrocyclization, metal-catalyzed enyne cycloisomerization as well as enyne metathesis, such scaffolds are interesting due to their widespread representation in natural products (Figure 5)[105] and the synthetic utility of such building blocks[106].

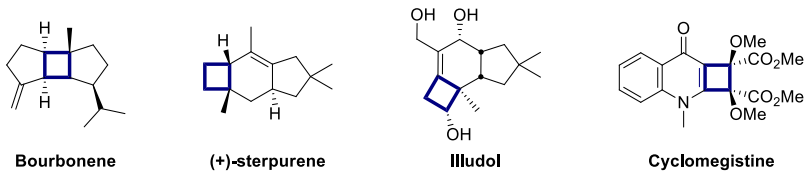
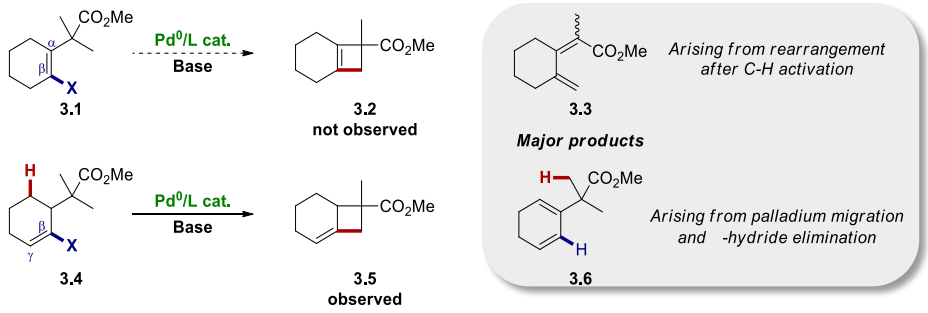


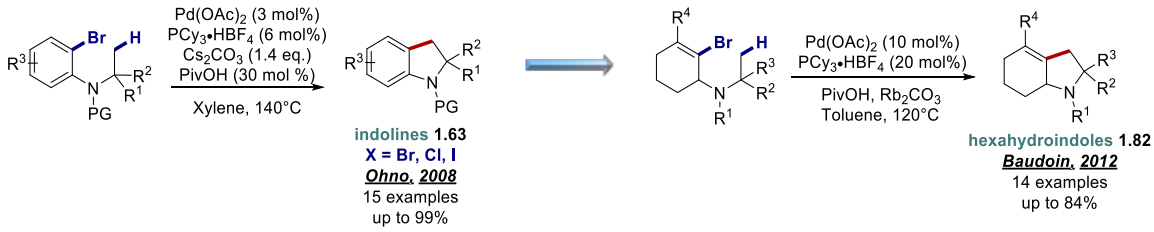
Figure 5 : *Examples of natural products containing a cyclobutene/cyclobutane moiety*

Thanks to lots of efforts devoted to the synthesis of precursors of C(sp^3)-H alkenylation **3.1-3.4,** initial results for this new strategy were obtained. Unfortunately, both substrates **3.1** and **3.4** mostly led to diene by-products **3.3** and **3.6**. First, exocyclic diene product **3.3** arises from electrocyclic ring-opening of the desired cyclobutene **3.2**. Afterwards, desired product **3.5** was observed by GC/MS analysis together with the endocyclic diene **3.6** arising from a C-H activation/palladium migration/β-hydride elimination sequence (Scheme 42). These results can be imputed to the high ring strain of the desired compounds.



Scheme 42 : *Initial attempts toward C(sp^3)-H alkenylation*

Taking advantage of these information and considering Ohno's synthesis of indolines[43], our group developed a straightforward access to hexahydroindoles **1.81** by intramolecular C(sp^3)-H alkenylation[67] (Chapter 1; paragraph 4.2.6) that we already applied to the total synthesis of aeruginosins[97, 104] (Chapter 2) (Scheme 43).



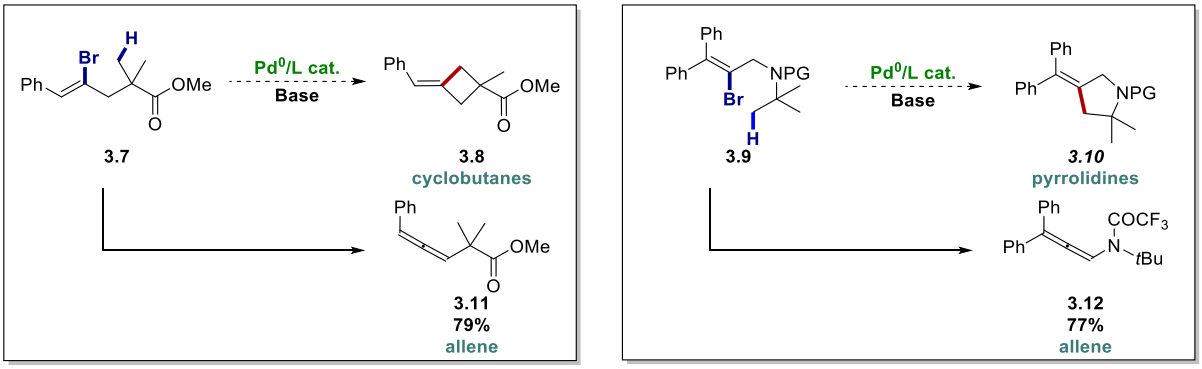
Scheme 43 : *Initial results using C(sp^3)-H alkenylation*

As an extension, we wondered if this concept could be as efficient in the case of acyclic bromoalkenes. Indeed, previously published work was limited to the formation of hexahydroindoles **1.82** containing a stereogenetic center in the precursor of C-H activation, thereby preventing the development of an enantioselective catalysis (Scheme 44). Such simplifications of the starting material represent an interesting entry to monocyclic products, which are prevalent scaffolds found in numerous bioactive natural molecules, through C-H activation. Indeed, all previous reported methodologies were limited to formation of bicyclic products (Chapter 1).

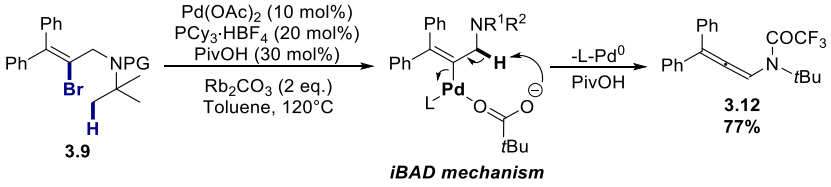
Scheme 44 : *Move to acyclic precursors of C-H activation*

At the outset of this study, our group turned his attention to cyclobutanes **3.8** and pyrrolidines **3.10** products as initial targets for our C-H activation strategy starting from the corresponding acyclic bromoalkenes **3.7**[107] and **3.9**[108]. However, classical reaction conditions only led to the obtention of allene by-products in both cases (Scheme 45 a.), via a plausible intramolecular base assisted deprotonation mechanism[109] (Scheme 45 b.). Interestingly, such by-reaction were not observed in the case of cyclic bromoalkene **1.81.** This can be imputed to the disfavored formation of highly strained endocyclic allenes.

a. Initials attempts

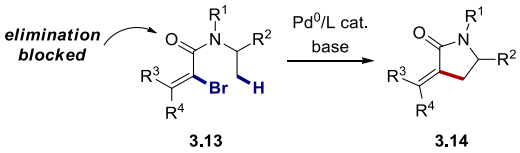


b. Plausible mechanism for allene formation



Scheme 45 :*Initial attempts for the formation of monocyclic compounds via C(sp*^{3}*)-H alkenylation*

Thanks to all these considerations, we have designed bromoalkene **3.13** which prevents elimination side-reactions and would provide a rapid access to γ-lactams derivatives (Scheme 46).



Scheme 46 : *Design of new acyclic precursors of C-H activation*

2. Development of a modular C(sp^3)-H alkenylation

2.1. Interest of α-alkylidene-γ-lactams

γ-lactams are important motifs found in numerous natural products such as (±)-clausenamide and salinosporamide A, which often present a high potential in medicinal chemistry. Accordingly, numerous synthetic approaches such as cyclization and cycloaddition/annulation reactions have been developed to obtain this structure in an efficient manner[110]. Of note, γ-lactams provide an entry to the synthesis of pyrrolidine alkaloids like broussonetines and plakoridines[111]. Interestingly, a few α-alkylidene-γ-lactams natural products were isolated, exhibiting cytotoxic antitumor and anti-inflammatory activities[112](Figure 6).

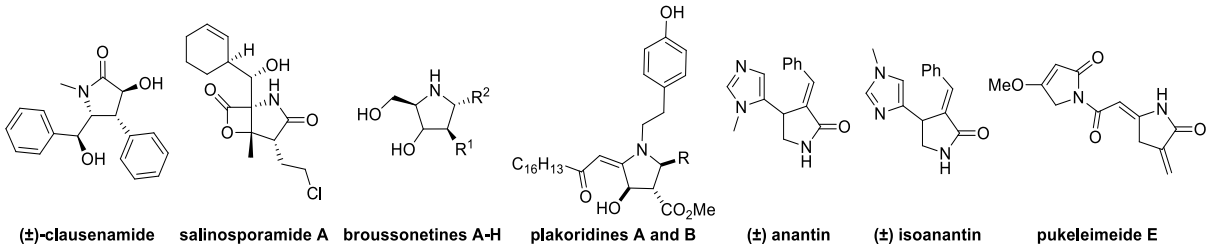
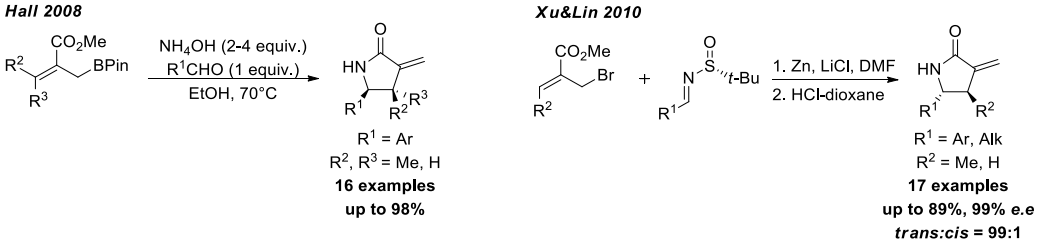


Figure 6 : *Examples of γ-lactams rings in natural products and derivatives thereof*

Unlike γ-lactams synthesis, access to a broad scope of α-alkylidene-γ-lactams remained relatively unexplored until last decade[113]. Nevertheless, some biological studies[112a, 112b, 114] have revived interest in accessing this moiety. Many synthetic approaches have been reported, but most of them suffer from severe scope limitation[115] or selectivity issues[116], thereby preventing the construction of a library of analogues for biological studies. Among all these synthetic strategies, the imine allylation strategy seems promising due to its broader scope and the relative simplicity of the process. While substitutions on the lactam core can be obtained with high selectivity, these processes are still limited to unsubstituted *exo*-methylene parts, thereby highlighting the interest to develop new approaches, in addition to the study of a new C-(sp^3)-H bonds transformation.



Scheme 47 : *Imine allylation/cyclization strategy for the synthesis of α-alkylidene-γ-lactams*

In addition to the growing interest for the synthesis of α-alkylidene-γ-lactams, this architecture was used as a platform for the elaboration of interesting heterocycles taking advantage of the intrinsic properties of the double bond and the α-β-unsaturated carbonyl moiety[115d, 116a, 117]. Moreover, thanks to the accessible carbonyl chemistry, subsequent ring-opening as well as partial or full reduction of the amide can be envisaged (Figure 7).

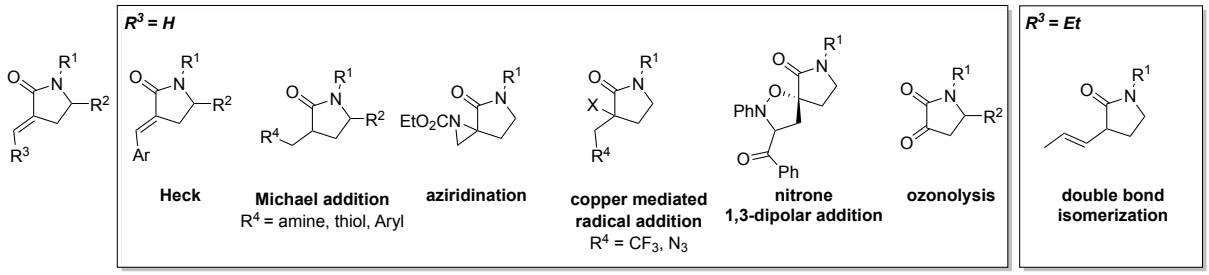
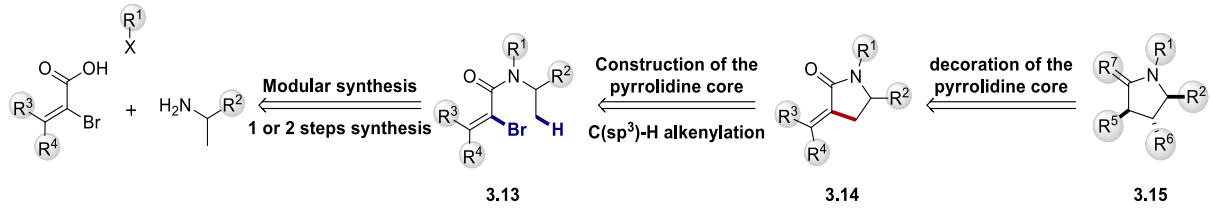


Figure 7 : *Overview of the synthetic utility of α-alkylidene-γ-lactams*

2.2. Modular synthesis of C(sp^3)-H alkenylation precursor

In order to prevent undesired side-reactions such as elimination reactions (Scheme 45), we have designed bromoalkene **3.13**. Interestingly, this precursor of C-H activation is readily accessible from commercially available starting materials such as amines, brominated carboxylic acids and electrophiles, thus allowing facile construction of various γ-lactam derivatives **3.14** after C-H activation. Thanks to the modular synthesis of α-alkylidene-γ-lactams **3.14**, fully-decorated products **3.15** can be envisioned after further functionalization (Scheme 48).

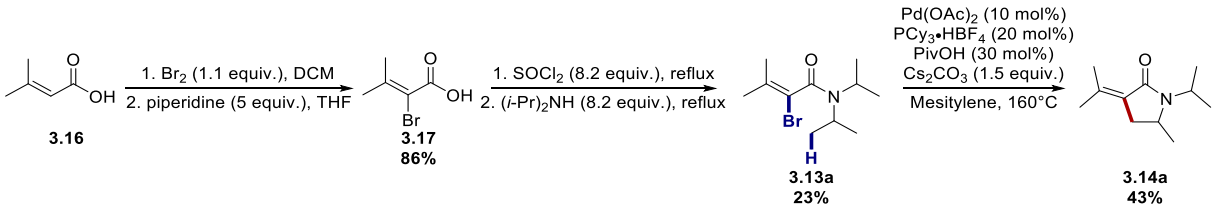


Scheme 48 : *Straightforward synthesis of γ-lactams thanks to modular synthesis*

2.1. Proof-of-concept

To evaluate the feasibility of this intramolecular C(sp^3)-H alkenylation, the reaction was first investigated on a simplified model substrate under classical conditions by the master student Janah Shaya[118] under the supervision of Dr. P. Holstein. Starting from the commercially available carboxylic acid **3.16**, dibromination followed by base-mediated elimination afforded the bromoalkene building block **3.17** in high yield. Amide bond formation between the corresponding acyl chloride of **3.17** and diisopropylamine yielded the precursors of C-H activation **3.13a** in low yield. After having tested various classical conditions for C-H

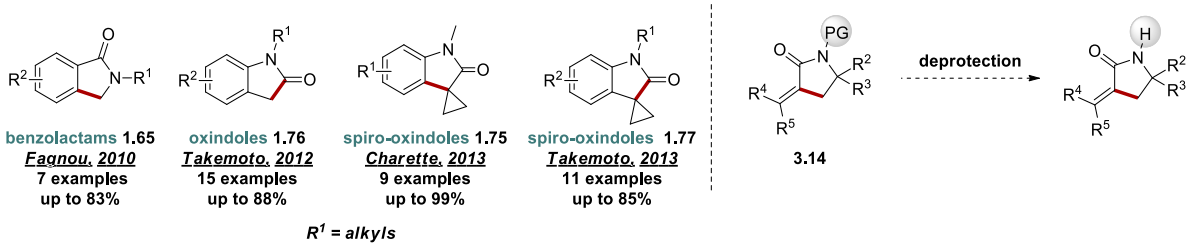
activation, the desired cyclized product **3.14a** was obtained in acceptable yield, thus providing a proof-of-concept for the cyclization of an acyclic substrate through palladium-catalyzed C(sp^3)-H alkenylation.



Scheme 49 : *Proof-of-concept for the cyclization of acyclic bromoalkene*

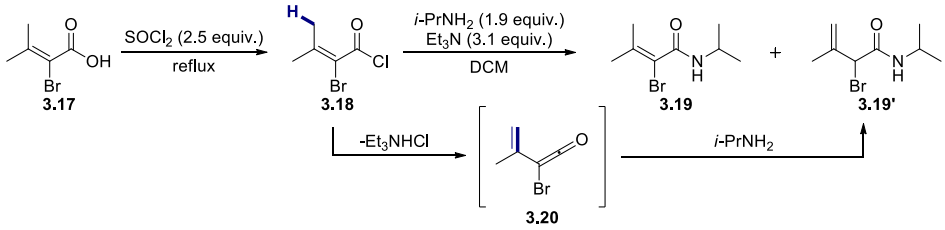
2.2. Optimization and generalization

At the outset of our study, we were seeking to develop a useful protocol to access functionalized γ-lactams. We were interested in designing substrates allowing access to the free *N*-H lactams. Indeed, previous methodologies relying on C(sp^3)-H activation were restricted to *N*-alkylated lactams [44 49 50-51], thereby limiting the synthetic utility of these latter. In order to overcome this limitation, we turned our attention to the design of *N*-protected amides which can potentially lead to the desired NH-lactams after deprotection. To circumvent potential side-reactions or degradation of the starting material, the protecting group should be stable under the reaction conditions applied and inert towards Pd-catalysis (no poisoning of the Pd-catalyst and no activated C-H bond). Moreover, it should be easily introduced and removed (Scheme 50).



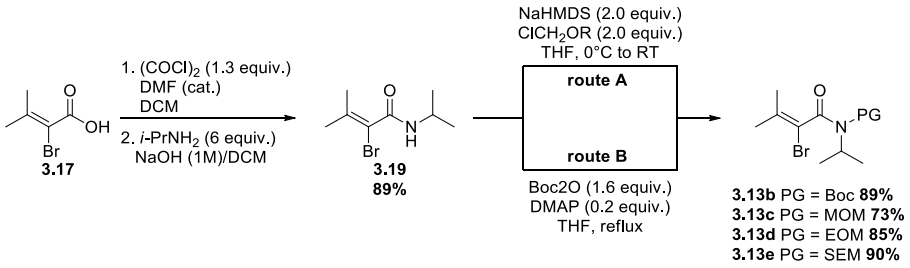
Scheme 50 :*Envisioned synthesis of N-H free γ-lactams*

In agreement with these considerations, we investigated both hemiaminal protecting groups which were already described to be competent in C-H activation[119], and Boc-group. Following the same procedure as before (***Scheme 49***), regioisomers **3.19** and **3.19'** were obtained as an inseparable mixture (Scheme 51). The latter was obtained from the formation of the ketene intermediate **3.20** (base-mediated) which was then trapped by the *iso*propylamine. This side-reaction can explain the low yield obtained for the synthesis of the amide **3.13a (*Scheme 49*).**



Scheme 51 : *Plausible pathway for the generation of by-product **3.19'***

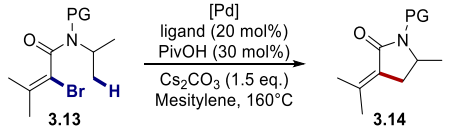
To overcome these limitations, we turned our attention to the optimization of the synthesis of amide **3.19**. We first changed the acyl chloride formation conditions using near-stoichiometric amount of oxalyl chloride with catalytic DMF. Then, we envisioned to use the biphasic Schotten-Baumann protocol to avoid the formation of by-product **3.19'**. Using this operationally simple and cheap procedure, formation of **3.19'** could be avoided and product **3.19** was obtained in high yield (89%). The major limitation of this protocol is that the amine has to be used in excess. This can be problematic in the case of expensive homemade amines or chiral amines. Of note, this procedure allows the multi-gram preparation of the desired amides, sometimes without purification. Finally, with the desired amide **3.19** in our hands, we carried out the synthesis of various *N*-protected amides **3.13b-e** using the two different routes shown below.



Scheme 52 : *Synthesis of the N-protected precursors of C-H activation*

With the required *N*-protected precursors of C-H activation **3.13b-e** in hand, we evaluated the compatibility of these protecting groups under the C-H activation conditions (Table 5). Whereas amide **3.19** was completely recovered when a Boc-group was used (entry1), low yield of cyclized products **3.14c-d** were observed by GC/MS analysis with MOM and EOM protecting groups respectively (entry 2-3). Nevertheless, after slight modifications of the reaction conditions, acceptable yield was obtained for EOM-substrate **3.13d** (entry 4). Interestingly, under the same conditions, the SEM-protected amide **3.13e** proved to be more efficient for the formation of the corresponding γ-lactam (entry 5).

Table 5 : *Evaluation of the protecting group*

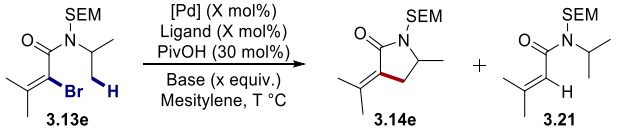


Entry	PG	[Pd] (mol %)	L	Yield %[a]
1	Boc	$Pd(OAc)_2$ (10)	PCy_3•HBF_4	0[b]
2	MOM	$Pd(OAc)_2$ (10)	PCy_3•HBF_4	15
3	EOM	$Pd(OAc)_2$ (10)	PCy_3•HBF_4	36
4	EOM	$[Pd(\eta^3\text{-allyl})Cl]_2$ (5)	PPh_2Et	57
5	SEM	$[Pd(\eta^3\text{-allyl})Cl]_2$ (5)	PPh_2Et	86 (73)

[a] *Yield estimated by GC/MS analysis using dodadecane as internal standard, isolated yield in bracket.* [b] *Only deprotection was observed*

Further optimization was performed using SEM-protected amide **3.13e** as a model substrate for the synthesis of potential *N*-H free γ-lactams. The following work was carried out by the master student Julien Vantourout under the supervision of Dr. Phillip Holstein[120]. Thanks to ^{1}H proton NMR and GC/MS analysis, hydrodebrominated compound **3.21** was identified as the major by-product, rendering the purification difficult due to its polarity which is close to the one of the desired product **3.14e**. Therefore, the process was optimized in order to obtain the highest possible yield with a good ratio between **3.14e** and **3.21**. Using previously described conditions as a starting point (entry 5; Table 5), carbonate bases such as potassium and rubidium carbonate were tried (entries 2-3), degrading both the efficiency and the **3.14e/3.21** ratio. Lowering the temperature strongly impacted the reaction course. Indeed, high amount of hydrodebrominated side-propuct **3.21** was observed at 150°C and 140°C (entries 4-5), thereby highlighting the crucial role of the energy required for the cyclization. Different phosphine ligands were tested. Similar diphenylphosphine ligands with methyl (entry 6) and cyclohexyl (entry 7) substituents instead of ethyl point out that steric bulk reduces the reaction efficiency. This is also verified in the trialkylphosphines' series. Whereas, trialkylphosphines were clearly less efficient than diphenylalkylphosphine ligands (entries 8-9), the bulkier PCy_3 phosphine provided a lower yield of **3.14e** than PEt_3 phosphine. Interestingly, the simplest triphenylphosphine proved to be the most efficient among all tested phosphines (entry 10), whereas modification of electronic properties of the phenyl ring resulted in sluggish reactions (entries 11-12). Afterwards, classical palladium sources were investigated (entries 13-15) providing lower or similar reactivities. Finally, the catalyst loading could be reduced to 2.5 mol% without alteration of the yield and chemoselectivity (entries 16-17) (Table 6).

Table 6 : *Optimization of the reaction conditions*



Entry	[Pd] (mol%)	Ligand (mol%)	Base	T (°C)	Ratio 3.14d/3.21	Yield %[a]
1	$[Pd(\eta^3\text{-allyl})Cl]_2$ (5)	PPh_2Et (20)	Cs_2CO_3	160	91:9	86 (73)
2	$[Pd(\eta^3\text{-allyl})Cl]_2$ (5)	PPh_2Et (20)	**K_2CO_3**	160	83:17	64
3	$[Pd(\eta^3\text{-allyl})Cl]_2$ (5)	PPh_2Et (20)	**Rb_2CO_3**	160	86:14	76
4	$[Pd(\eta^3\text{-allyl})Cl]_2$ (5)	PPh_2Et (20)	Cs_2CO_3	**150**	79:21	73
5	$[Pd(\eta^3\text{-allyl})Cl]_2$ (5)	PPh_2Et (20)	Cs_2CO_3	**140**	46:54	20
6	$[Pd(\eta^3\text{-allyl})Cl]_2$ (5)	**$PPh_2Me{\cdot}HBF_4$** (20)	Cs_2CO_3	160	84:16	78
7	$[Pd(\eta^3\text{-allyl})Cl]_2$ (5)	PPh_2Cy (20)	Cs_2CO_3	160	32:68	22
8	$[Pd(\eta^3\text{-allyl})Cl]_2$ (5)	PEt_3 (20)	Cs_2CO_3	160	41:59	35
9	$[Pd(\eta^3\text{-allyl})Cl]_2$ (5)	PCy_3 (20)	Cs_2CO_3	160	47:53	22
10	$[Pd(\eta^3\text{-allyl})Cl]_2$ (5)	PPh_3 (20)	Cs_2CO_3	160	92:8	91 (81)
11	$[Pd(\eta^3\text{-allyl})Cl]_2$ (5)	$P(p\text{-}NMe_2\text{-}C_6H_4)_3$ (20)	Cs_2CO_3	160	86:14	49
12	$[Pd(\eta^3\text{-allyl})Cl]_2$ (5)	$P(p\text{-}CF_3\text{-}C_6H_4)_3$ (20)	Cs_2CO_3	160	-	0 [b]
13	$PdCl_2$ (10)	PPh_3 (30)	Cs_2CO_3	160	76:24	65
14	$Pd(OAc)_2$ (10)	PPh_3 (30)	Cs_2CO_3	160	76:24	67
15	$Pd_2(dba)_3$ (5)	PPh_3 (20)	Cs_2CO_3	160	91:9	81
16	$[Pd(\eta^3\text{-allyl})Cl]_2$ **(2.5)**	PPh_3 (10)	Cs_2CO_3	160	92:8	91 (83)
17	$[Pd(\eta^3\text{-allyl})Cl]_2$ **(1.25)**	PPh_3 (5)	Cs_2CO_3	160	84:16	79

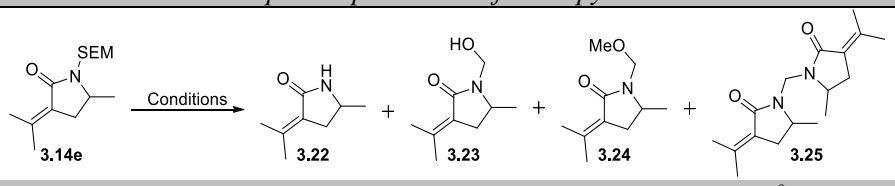
[a] *Yield estimated by GC/MS analysis, using tetradecane as internal standard, isolated yield in bracket.* [b] *Only 20% conversion was observed*

2.3. Deprotection of the SEM-substrate

In order to develop a methodology with high synthetic utility, we turned our attention to the obtention of the free NH-lactam **3.22** through cleavage of the SEM-protecting group, which is widely used for the protection of alcohols and amines. Various deprotection conditions involving fluorine sources and Brønsted or Lewis acids were developed[121], since its introduction by Lipshutz and coworkers[122]. Whereas the SEM deprotection of alcohol is efficient and reliable, the cleavage of the *N*-SEM bond can be tricky for some substrates[123]. Indeed, we were unable, under various conditions, to detect the slightest trace of the desired deprotected compound **3.22** (Table 7). We first tried the classical TBAF[122, 124] reagent for such cleavage. Surprisingly, no conversion was observed (entry 1). Then, we turned our attention to Brønsted acids such as HCl, H_2SO_4 or TFA under various reactions conditions (entries 2-4). Whereas full conversion was observed in all cases, we were able to observe compounds **3.23**, **3.24** and **3.25** respectively in high quantities by GC/MS analysis. The formation of these unexpected compounds can be explained thanks to the mechanism proposed in Scheme 53. They certainly arise from the pivotal electrophilic intermediate **3.26**, which is obtained via acid-mediated elimination. Interestingly, dimer **3.25** should come from the reaction between **3.22** and intermediate **3.26,** thus providing a promising evidence for the formation of desired free

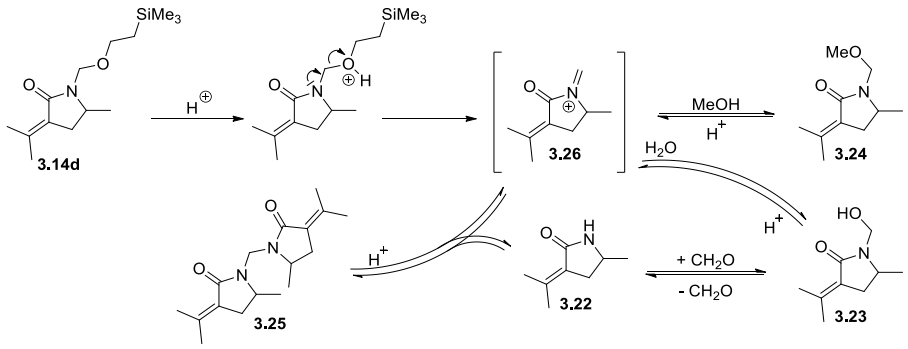
NH-lactam **3.22**. Unfortunately, different Lewis acids (entries 5-7) which already proved to be efficient in laborious cases[123a, 125], were completely inefficient on our substrate **3.14e** leading to the formation of the *N*-hydroxymethyl compound **3.23**. Nevertheless, this latter is stable enough to be isolated[126], thus providing an alternative pathway toward product **3.22**. Indeed, *N*-hydroxymethyl compounds can be deprotected via formaldehyde elimination under high vacuum and temperature[126], heating under basic conditions [124, 127] or with a trapping agent [128]. At this stage, further investigations should lead us to the desired product **3.22**.

Table 7 : *Attempted deprotection of SEM-pyrrolidinone* ***3.14e***



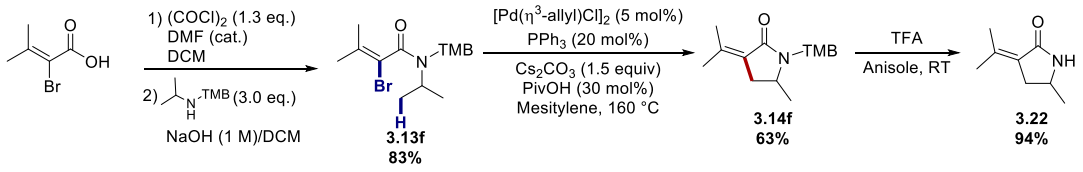
Entry	Reagent	equiv.	t (h)	T(°C)	Solvent	conv.	Ratio[a] 3.22/3.23/3.24/3.25
1	TBAF	5	24	reflux	THF	0	-/-/-/-
2	HCl	1	24	RT	Et_2O	>99	0/80/0/10
3	H_2SO_4	0.03	3	RT	THF/MeOH	>99	0/0/100/0
4	TFA	630	3	RT	DCM	>99	0/0/0/100
5	$SnCl_4$	14	4	0 to RT	DCM	>99	0/89/1/9
6	$AlMe_3$	5	2	-78°C to RT	DCM	>99	0/100/0/0
7	$AlMe_2Cl$/DIPEA	5	2	-78°C to RT	DCM	>99	0/100/0/0

[a] *Ratio estimated by GC/MS analysis*



Scheme 53 : *Plausible mechanism for the formation of compounds* ***3.23-25***

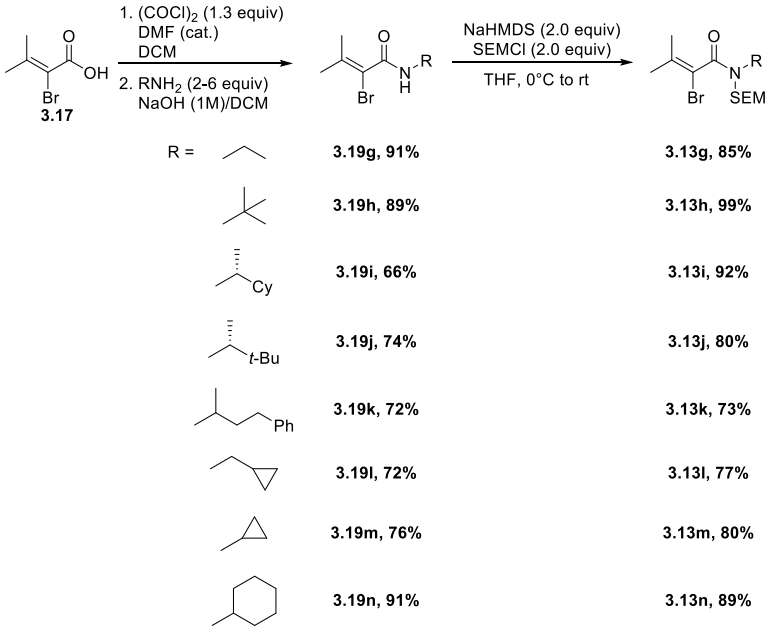
In parallel, we sought to find a new protecting group efficient in catalysis and easily cleavable. In this regard, we selected the TMB group already employed by Cramer and coworkers in palladium(0)-catalyzed C-H activation. Gratifyingly, we were able to obtain the cyclized product **3.14f** in good overall yield as well as the desired free NH-lactam **3.22** using classical conditions for the deprotection of the TMB protecting group[64], thus highlighting the synthetic utility of this new protocol.



Scheme 54 : *Access to the free NH-γ-lactams* ***3.22***

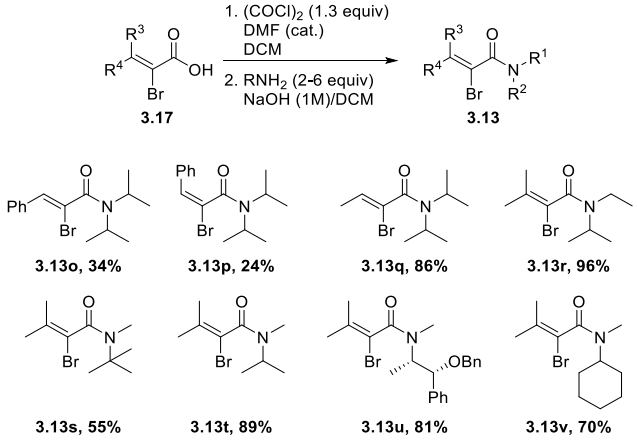
2.4. Synthesis of acyclic precursors of C-H alkenylation

At the outset of this study, we were confident, due to numerous reports, about the possibility to deprotect the SEM-group on the γ-lactam derivative. Thus, we focused on the evaluation of the reaction scope. In this regard, we carried out the synthesis of diversely substituted SEM-amides **3.13** using the Schotten-Baumann procedure previously used (Scheme 52). Taking advantages of this simple protocol, we were able to obtain precursors of C-H activation **3.13g-n** in excellent yield (Scheme 55).



Scheme 55 : *Synthesis of SEM-protected amides* ***3.13g-n***

In addition, dialkylated substrates **3.13o-w** were prepared in good yield, thus providing access to a broader scope. Precursors **3.13o-p** were both synthetized from an *E/Z*-mixture of the corresponding carboxylic acids, thus explaining the lower yield obtained for these substrates (Scheme 56).

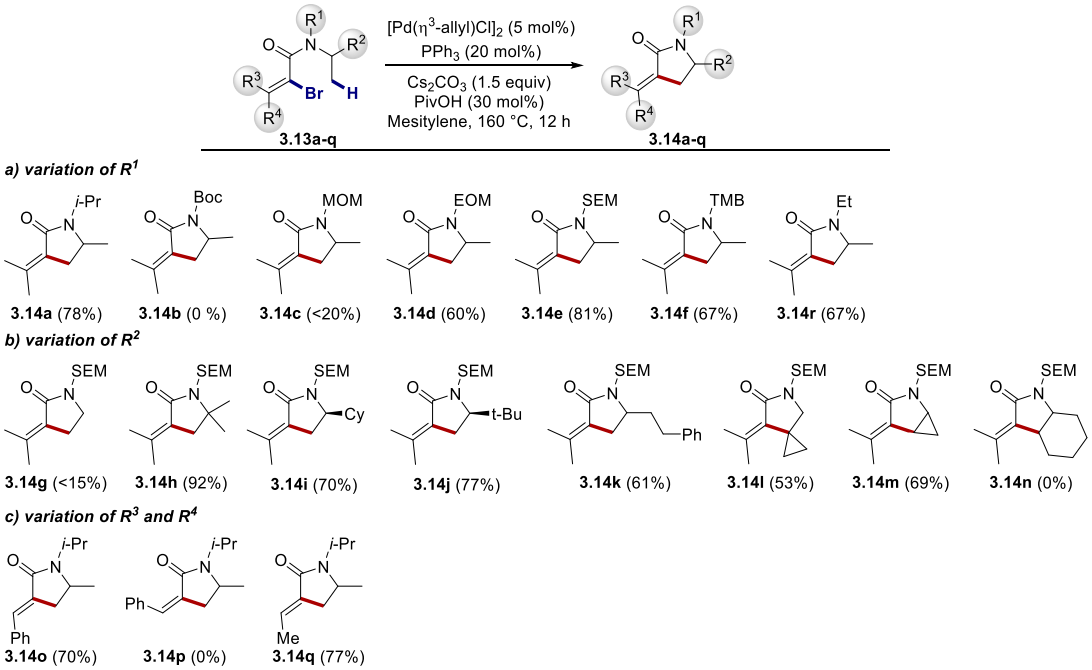


Scheme 56 : *Synthesis of dialkylated amides* ***3.13o-w***

2.5. Scope and limitations of the intramolecular C(sp^3)-H alkenylation

With the precursors of C-H activation in our hands, we explored the scope and limits of this new intramolecular C(sp^3)-H alkenylation. First, the nitrogen substituent was varied. As mentioned before, the reaction tolerated aminals **3.14c-e**, alkyl groups **3.14a-3.14r** in addition to the TMB group **3.14f** and the respective γ-lactams were obtained in good yield. Somewhat surprisingly, the *N*-isopropyl group of substrate **3.13r** (R^1 = Et, R^2 = Me) underwent C–H activation selectively with regard to the less hindered *N*-ethyl group (**3.14r**). This points out an atypical behavior of the current acyclic bromoalkenes compared to previously studied substrates (Scheme 16 & Scheme 17). Then, we examined the nature of the alkyl groups undergoing C-H activation. First, ethyl-substrate **3.14g** provided low amounts of the desired product together with a lot of protodebrominated product **3.21g** (GC/MS area ratio 3.14g:3.21g 14:86), thereby confirming the lack of reactivity of linear alkyl groups in the current system (see also **3.14r**). Compound **3.13h** containing the bulkier *tert*-butyl group was almost totally converted to the desired cyclized product **3.14h** (92%). The reactivity trend **3.14g**<**3.14e**<**3.14h** corresponds to one observed for previously reported C(sp^3)-H activation systems. This impact on the reaction efficiency can be imputed to the Thorpe-Ingold effect as well as a statistic effect. Starting from commercially available enantiopure amines, chiral lactams **3.14i-j** could be synthetized without any racemization. Interestingly, selective activation/cyclization of **3.13k** gave rise to **3.14k**, even in presence of competitive C-H bonds. Finally, activation of unactivated secondary C-H bonds was found to be unsuccessful. However, functionalization of more activated methylene and even methine C-H bonds of cyclopropyls provided the corresponding spirocyclic γ-lactam **3.14l** and fused γ-lactam **3.14m** in good yield. Then, the reactivity of bromoalkenes with a trisubstituted double bond was also examined.

Surprisingly, whereas *Z*-configured bromoalkenes **3.13o&3.13q** underwent cyclization to furnish the corresponding *E*-products **3.14o&3.14q** in high yield, *E*-isomers of **3.13o** (**3.13p**) was found to undergo rapid base-promoted elimination to give the corresponding alkyne. Thanks to control experiments, we found out that this side-reaction occurred even in the absence of a palladium catalyst and selectively for the *E*-configured bromoalkene **3.14p**, which is unexpected due to the relative syn-position of the hydrogen and bromine. It would be interesting to conduct further investigations to get a better understanding of the factors controlling this side-reaction.

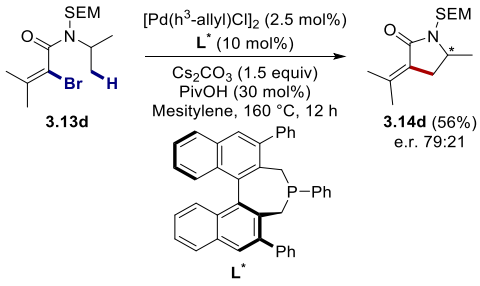


Scheme 57 : *Scope, limitations and selectivity pattern of the intramolecular C-H activation*

2.6. Evaluation of feasibility for an enantioselective version

At this stage, we evaluated the possibility to obtain enantioenriched compounds. At the outset of this study, the enantioselective discrimination of two enantiotopic methyl-groups were mostly achieved using a chiral ancillary ligand (paragraph 4.2.5 of Chapter1). Thus, we turned our attention to P-arylbinepine ligands which can be considered as chiral analogues of PPh_3. Indeed, these are often considered as chiral surrogates for trialkylphosphines. Precise electronic and steric properties of a seriees of binepine ligands were measured and calculated by our group[60-61], thereby demonstrating the analogy between P-arylbinepine and PPh_3. After screening of different P-arylbinepine ligands, we found out that the ligand **L*** was competent to obtain moderate yield and acceptable enantioinduction (Scheme 58). The enantioselective version of this C(sp^3)-H activation was not the purpose of this study but this preliminary result

constitutes a proof-of-concept for the preparation of enantioenriched compounds via C(sp^3)-H alkenylation.



Scheme 58 : *Proof-of-concept for the enantioselective C(sp^3)-H alkenylation*

2.7. Attempts toward a total synthesis of plakoridine A

2.7.1. Introduction

We were interested in applying our methodology to natural products synthesis. For this purpose, we selected plakoridine A as an initial target. Plakoridine A belongs to a family of three racemate members isolated from a marine sponge of the genus *Plakortis* in Okinawa, Japan, all characterized by an hexadecyl chain. Plakoridine A and B are structurally related pyrrolidines, while plakoridine C is a piperidine alkaloid[129](Figure 8).

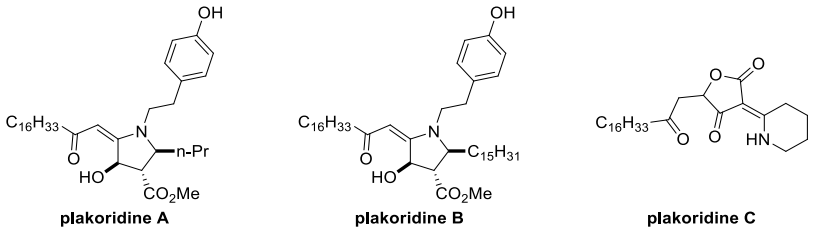
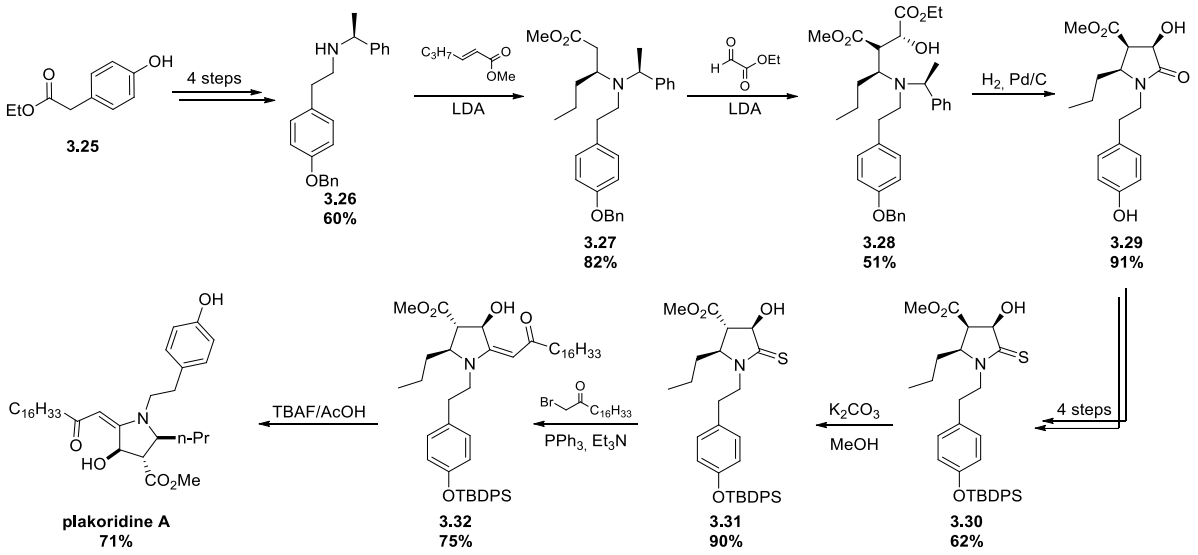


Figure 8 : *Structure of plakoridine A, B and C*

Up to now, a single asymmetric total synthesis of (2*S*,3*S*,4*R*)-plakoridine A was reported by Ma and coworkers[130]. Based on the chiral auxiliary approach developed by Davies and coworkers[131], they achieved the synthesis of enantiopure plakoridine A in fourteen steps with an overall yield of 3%. Thanks to this total synthesis, they confirmed that natural plakoridine A is a racemate, which is consistent with Whitehead's assumption based on a biomimetic synthesis[132]. Using a four-steps sequence, they obtained the chiral secondary amine **3.26** from commercially available ester **3.25**, in good overall yield. A diastereoselective Michael reaction and sequential diastereoselective aldolisation furnished the enantiopure compound **3.28** after isolation of this latter from other diastereoisomers. Under hydrogenolysis conditions, *in situ* generation of the secondary amine prompted the desired cyclization to afford the γ-lactam **3.29** with concomitant cleavage of the benzyl protecting group. A four-steps sequence led to the formation of the thiolactam **3.30** in good overall yield.

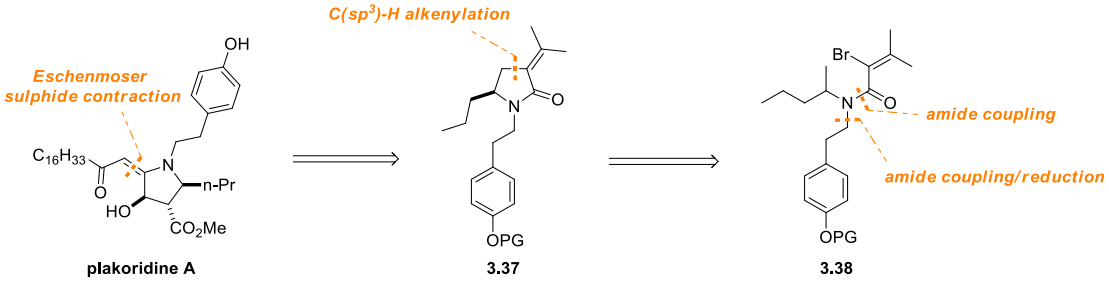
Thanks to a base-mediated epimerization, the thermodynamically more stable thiolactam **3.31** was obtained. Finally, Eschenmoser sulfide contraction and deprotection furnished plakoridine A (Scheme 59).



Scheme 59 : *Enantioselective total synthesis of plakoridine A.*

2.7.2. Retrosynthetic analysis

The C16 aliphatic tail will be introduced through the Eschenmoser sulphide contraction reported by Ma (Scheme 59), thus leading to crucial γ-lactam **3.37**. This latter should be accessible thanks to the C(sp^3)-H alkenylation methodology developed in this study. Finally, the amide **3.38** with appropriate substituents will be prepared using classical organic reactions (Scheme 60).

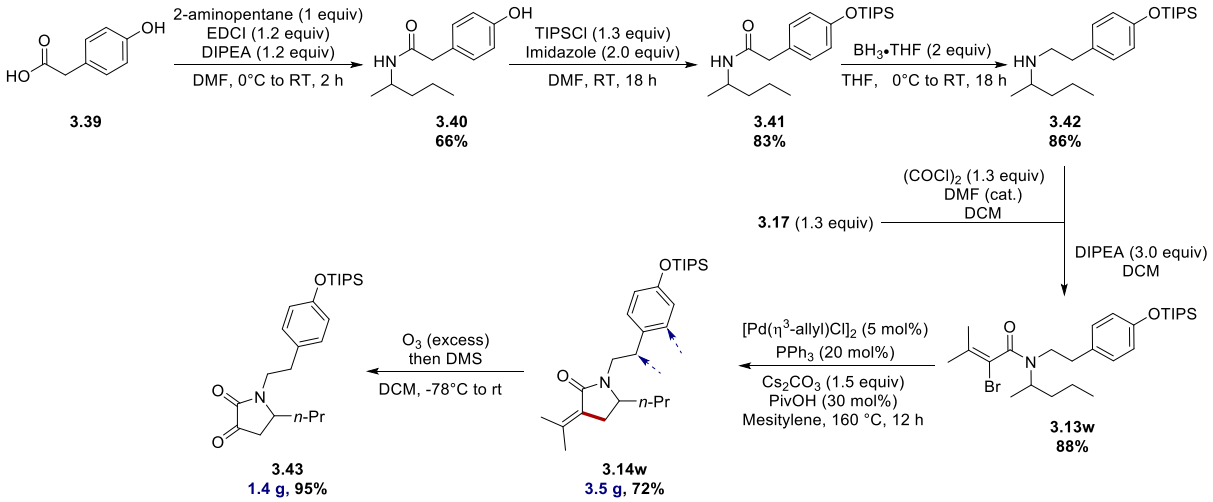


Scheme 60 : *Our retrosynthetic plan for the synthesis of plakoridine A*

2.7.3. Unsuccessful synthesis of plakoridine A

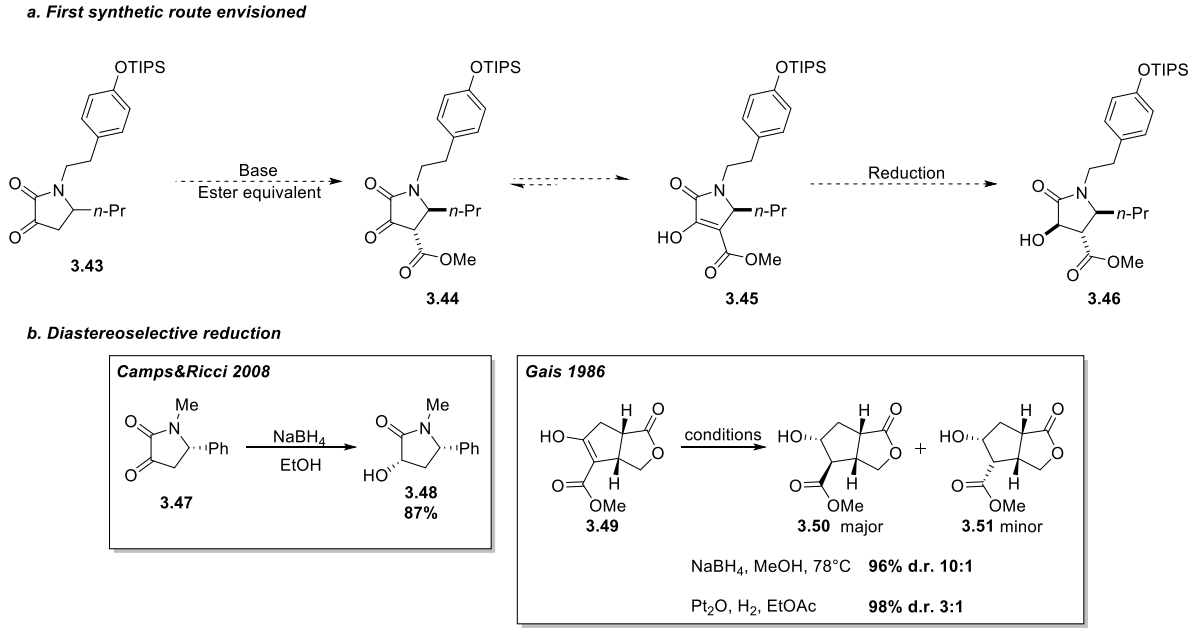
First, we focused our attention to the synthesis of the precursor of C-H activation **3.13r**. Starting from commercially available compound **3.39**, a peptide coupling with 2-aminopentane followed by protection of the phenol residue allowed the formation of the amide **3.41** in good yield. Then, a two-steps sequence involving an amide reduction and the improved Schotten-Baumann protocol (Scheme 52) furnished the desired compound **3.13w** in acceptable yield.

Gratifyingly, under our optimized conditions for C-H activation, we were able to achieve multi-gram synthesis of **3.14w** with a remarkable site-selectivity for the desired primary C-H bond even in presence of more activated benzylic and (Csp^2)-H bonds (multi-gram preparation of compound **3.14w** was performed by Dr. Anthony Millet) (Scheme 61).



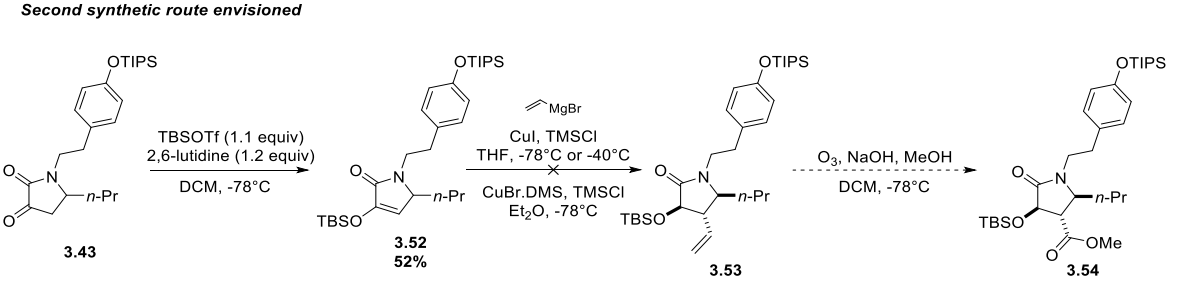
Scheme 61 : *Synthesis of the pyrrolidine core of plakoridine A*

Finally, α-ketolactam could be yielded using classical ozonolysis, thus furnishing more than 1 gram of **3.43 (**Scheme 61). This latter was found to be unstable on silica gel or alumina, thus precluding flash chromatography. Such a behaviour for α-ketolactams was already reported independently by Rapoport and Carlson[133]. In particular, they were able to identify self-condensation which provides a dimeric side-product as a major issue. Nevertheless, we turned our attention to the installation of the required ester moiety. First, we envisaged to insert this latter through C-alkylation under basic conditions using an ester equivalent. This would furnish compound **3.44** in equilibrium with its enol-form **3.45**. Considering literature elements [134] (Scheme 62 b), we assumed that reduction would lead to compound **3.46** with good diastereo- and chemoselectivity (Scheme 62 a).



Scheme 62 : *Envisioned route to advanced intermediate* ***3.46***

Unfortunately, we were unable to obtain the desired *C*-alkylated product **3.44**. Indeed, reactions between the corresponding enolate and soft equivalents of methyl-ester such as Mander's reagent[135], 1*H*-Imidazole-1-carboxylate[136] or methyl pentafluorophenyl carbonate[137], provided only degraded compounds. Further investigations on the enolate formation (hard/soft base[138], solvent, temperature, additive) were unsuccessful. Moving to hard electrophiles, such as methyl chloroformate, led to the exclusive formation of the expected but undesired *O*-alkylated product. We thus envisioned an alternative route to access the advanced intermediate **3.46** in an efficient manner. We turned our attention to the synthesis of compound **3.52** which can be considered as a Michael acceptor. We thus assumed that 1,4-addition of vinyl cuprate followed by ozonolysis in methanolic sodium hyodroxide[139] would give access to the compound **3.54**. Whereas compound **3.52** can be obtained in acceptable yield, Michael addition of the *in situ* generated vinyl cuprate was found to be inefficient, thus leading us to give up the total synthesis of plakoridine A (Scheme 63).

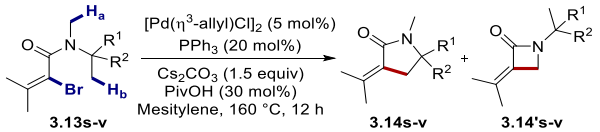


Scheme 63 : *Envisioned conjugate addition route*

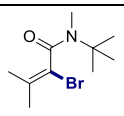
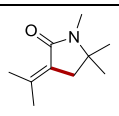
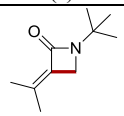
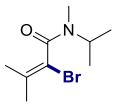
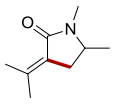
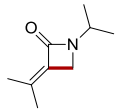
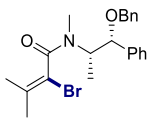
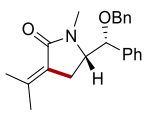
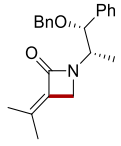
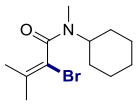
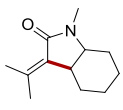
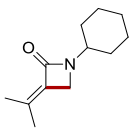
2.8. Selectivity of the activation of primary C-H bonds

During the extension of the reaction scope, we studied the selectivity in the activation of non-equivalent primary C-H bonds starting from reactants **3.13s-v**. In all cases, these reactants should give access to γ-lactams **3.14s-v** or highly strained β-lactams **3.14's-v**. First, a complete selectivity for the formation of the γ-lactam **3.14s** over the β-lactam **3.14s'** was observed. This is somewhat surprising since the activation occurs preferentially via the smaller palladacycle intermediate for aromatic substrates. Nevertheless, this result is in line with the selectivity obtained for the compound **3.14r**. Indeed, this latter also afforded selectively γ-lactam **3.14r** over β-lactams **3.14r'** (methylene activation). Interestingly, when substrate **3.13t** is submitted to the reaction conditions, a separable mixture of γ- and β-lactams was observed. Moreover, in the case of substrate **3.13u**, decreasing the population of H_b resulted in the selective formation of the corresponding β-lactam **3.14u'** in acceptable yield with concomitant protodebrominated side-product **3.21u**. Finally, as expected from the lack of reactivity of methylene bonds and previous observations concerning compounds **3.14r** and **3.14n**, a complete selectivity for the formation of β-lactam **3.14v'** was observed (*Table 8*).

***Table 8** : Selectivity of the activation of primary C-H bonds*



3.13s-v → **3.14s-v** + **3.14's-v**

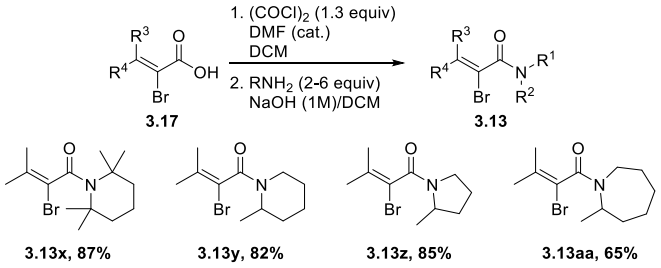
Entry	Reactant	Product(s)[a]	3.14/3.14'[b]
1	 **3.13s**	 **3.14s** (92%)  **3.14s'** (0%)	>98:2
2	 **3.13t**	 **3.14t** (38%)  **3.14t'** (11%)	71:29[c]
3	 **3.13u**	 **3.14u** (<5%)  **3.14u'** (47%)	7:93[c]
4	 **3.13v**	 **3.14v** (<5%)  **3.14v'** (40%)	<2:98[c]

[a] *Yield of isolated product in parentheses* [b] *Determined by GCMS analysis of the crude mixture*
[c] *The corresponding protodebrominated products **3.21s-v** were also formed in the following GC ratios : **3.14t/3.14t'/3.21t** 53:22:25; **3.14u/3.14u'/3.21u** 5:63:32; **3.14v'/3.21v** 48:52.*

2.9. Construction of bicyclic γ-lactams

2.9.1. Introduction and synthesis of precursors of C-H activation

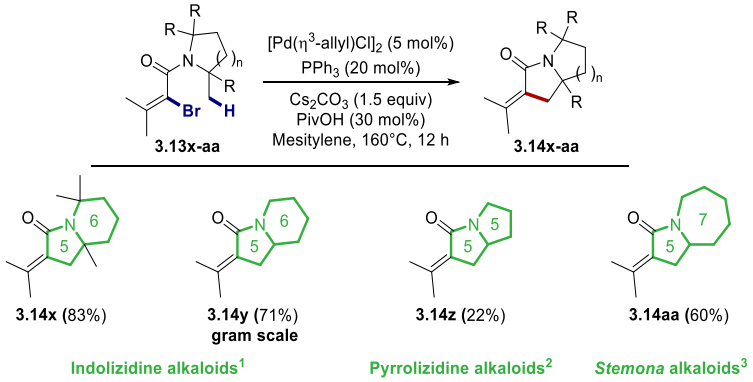
Next, the reactivity of monocyclic precursors, relevant to the synthesis of bicyclic alkaloids was studied. The flexible Schotten-Baumann protocol allowed the synthesis of 5-,6- and 7-membered ring precursors **3.13w-z** in an efficient manner (Scheme 64).



Scheme 64 : *Synthesis of C-H activation precursors* ***3.13x-aa***

2.9.2. Scope and limitations

In general, desired bicycles **3.14x-aa** were obtained in good yield except in the case of the 5,5-bicyclic ring **3.14z** most likely due to ring strain. Moreover, no side-product arising from the activation of methylene C-H bonds adjacent to the nitrogen was observed. Gratifyingly, the scale-up synthesis of product **3.14y** was achieved in a reproducible manner, thus leading us to envision the total syntheses of indolozidine alkaloids (Scheme 65).

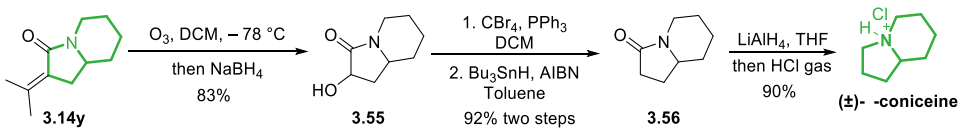


Scheme 65 : *Construction of bicyclic γ–lactams through C-H activation*

2.9.3. Application to alkaloid synthesis

Interestingly, these lactams can be viewed as an entry-platform to the synthesis of pyrrolidine[111b], pyrrolizidine [140], indolizidine [141], and Stemona alkaloids[142] (Scheme 65). For instance, we focused our attention to the total synthesis of (±)-*δ*-coniceine. Thanks to a reductive ozonolysis, an inconsequential mixture of diastereoisomers of **3.55** was obtained in good yield. Of note, these latter should provide an access to poly-hydroxylated indolozidines[143]. Instead, we obtained after an Appel reaction and a radical reductive debromination the lactam

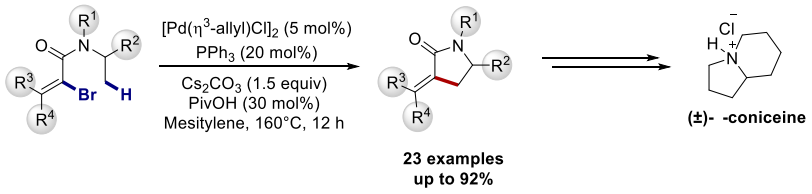
3.56. Finally, reduction of the amide resulted in the obtention of the completely saturated system, which was then protonated to furnish the total synthesis of (±)-δ-coniceine hydrochloride salt in good overall yield (Scheme 66).



Scheme 66 : *Total synthesis of (±)-δ-coniceine*

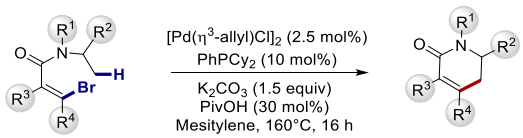
3. Conclusion

In summary, we have developed a new straightforward access to α-alkylidene-γ-lactams via C(sp^3)-H alkenylation. Starting from easily available C-H activation precursors, this new methodology allows to obtain a broad range of γ-lactams by modification of R^1-R^4 groups. Interestingly, compared to previous syntheses of amide derivatives by C(sp^3)-H activation, the free-NH lactams can be obtained after removal of the TMB group. Moreover, these lactams can be used as valuable building blocks as demonstrated by the synthesis of the indolizidine alkaloid (±)-*δ*-coniceine and of a plakoridine A precursor. In addition, a highly enantioselective version can be envisaged thanks to the preliminary result obtained. An extensive screening of ligands as well as reaction conditions could lead to highly enantioenriched α-alkylidene-γ-lactams.



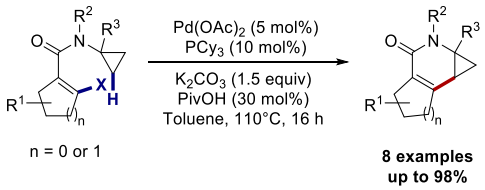
Scheme 67 : *Overview of the α-alkylidene-γ-lactams synthesis via C(sp^3)-H alkenylation*

During the course of this study, the extension of this methodology to δ-lactams was initiated in our group by the master student Maria Vogler. Unfortunately, after many efforts devoted to the optimization of the reaction conditions, the scope of the reaction was found to be limited to few examples, thereby illustrating the difficulty to obtain 6-membered ring through C-H activation. (Scheme 68).



Scheme 68 : *Extension to δ-lactams*

Few months later, Charette and coworkers described an extension of this C(sp^3)-H alkenylation based on the activation of relatively close substrates studied in our group. Thanks to well-designed precursors of C-H activation, they developed a new route to 5-6-3 and 6-6-3 cyclopropyl-fused azacycles through activation of cyclopropanes C-H bonds, thereby demonstrating the synthetic utility of this strategy (Scheme 69).



Scheme 69 : *Extension of the C(sp^3)-H alkenylation scope*

Chapter 4

Synthesis of β-Lactams by Palladium(0)-Catalyzed C(sp^3) Carbamoylation

1. Introduction

1.1. Interest of β-lactams

Naturally-occuring β-lactam compounds may be classified into four subfamilies, namely as the penicillin/cephalosporins, the clavams, the carbapenems and the monocyclic β-lactams, depending on their structural properties and the mechanism of their biosynthesis. The first isolated β-lactams (*i.e.* the penicillin and the cephalosporin C) were both accidentally discovered from the fermentation of filamentous fungi. Moreover, they rapidly shown interesting activity as antibacterial drugs, thus engendering numerous biological studies and the synthesis of various β-lactam compounds and analogues. Nowadays, β-lactam antibiotics account for 65% of the total world market of antibiotics (20 billion dollars per year)[144] (Figure 9).

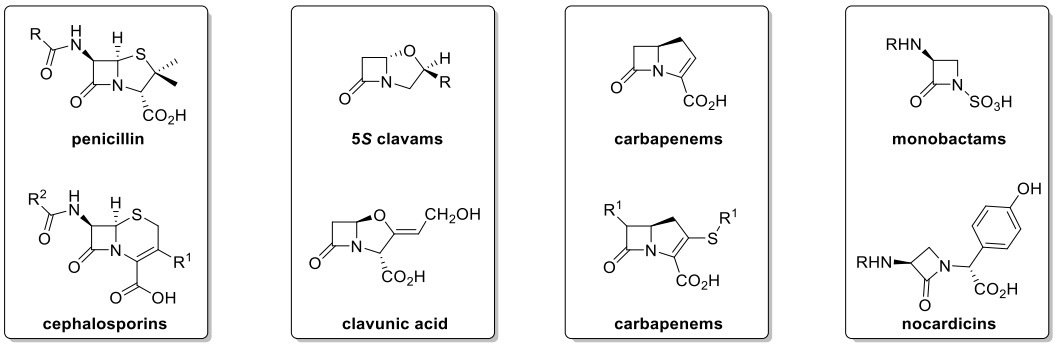
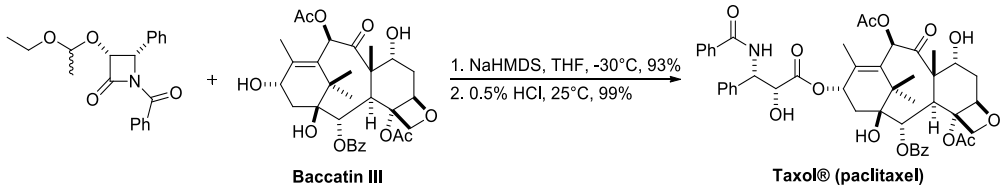


Figure 9 : *Subfamilies of β-lactam compounds*

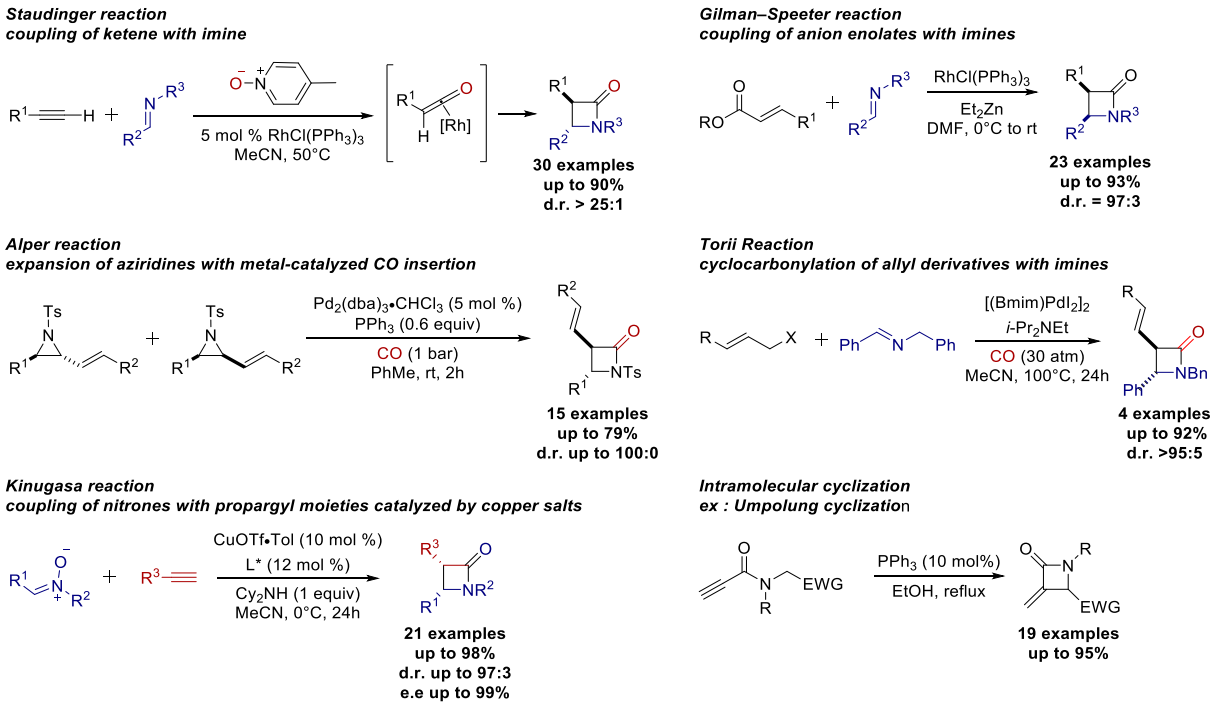
In addition to their biological interest, β-lactams are valuable synthons in organic synthesis. Indeed, thanks to the ring strain of the 2-azetidinone core, selective ring opening can be achieved leading to α- and β-amino acids, peptidomimetic compounds or complex natural products. Of note, this strategy is employed in the highly efficient last synthetic step to well-known Taxol® anticancer agent[145] (Scheme 70).



Scheme 70: *β-lactam as acylating reagent of Baccatin III*

1.2. Classical organic syntheses of β-lactams

Due to these unique biological properties and synthetic utility, many efforts were devoted to deliver the 2-azetidinone core in an efficient manner. Among these synthetic approaches, the Staudinger reaction[146], the Gilman-Speeter reaction[147], the Alper reaction[148], the Kinugasa reaction[149], the Torii reaction[150] as well as intramolecular cyclization[151] are the most widely used because of their efficiency. These synthetic methodologies are highlighted below with recent examples from the literature[152] (Scheme 71).

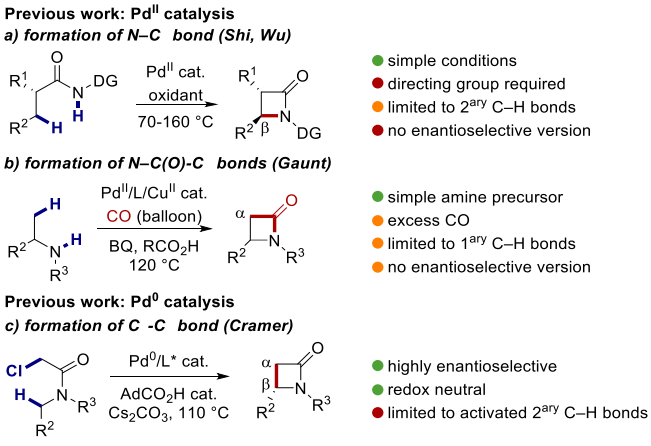


Scheme 71 : *Selected strategies to access β-lactam scaffolds*

2. Synthesis of β-lactams by C(sp^3)-H functionalization

Inspired by the pioneering results of Corey and coworkers[153], using C-H insertion via photo-decomposition of a diazo intermediate in their synthesis of penicillin, numerous transition-metal catalyzed[152, 154] or transition-metal-free[152, 155] C-H insertion methodologies were developed to access β-lactams and derivatives. Whereas this strategy is well-employed, methodologies to access β-lactams via C(sp^3)-H bonds activation are still limited and suffer from some limitations. The first approach was inspired by the synthesis of azetidines developed by the groups of Daugulis and Chen[156], based on Pd^{II}/Pd^{IV} C-H activation using picolinamide as bidentate directing groups. Using respectively the PIP or the 8-aminoquinoline directing group, the groups of Shi[157] and Wu[158] were able to access β-lactams through the formation of

the N–C_β bond, thanks to a fine-tuning of the required stoichiometric oxidant. Whereas this approach is operationally simple, extra-steps are required for the installation and removal of the directing group, thereby potentially limiting its synthetic utility. Moreover, these methodologies were at that time restricted to the activation of methylene C-H bonds and the development of an enantioselective version should be limited by the bidentate nature of the directing group. Taking advantages of previously reported conditions as a starting point and reconsidering the mechanism of carbonylative C-H activation[159], Gaunt and coworkers described a new protocol to access β-lactams via the direct carbonylation of simple aliphatic amines using Pd^{II}-Pd^{0}-Pd^{II} catalysis[160]. Under an excess of CO (balloon) and with an oxidative system (Cu^{II} as co-catalyst and benzoquinone (BQ) as terminal oxidant) to regenerate *in situ* the Pd^{II} catalyst, they found that a sterically hindered carboxylic acid in combination with a nitrogen ligand are required to obtain an efficient process. Limited to the activation of primary C-H bonds, the reaction shows a broad scope with particularly good yield for unhindered aliphatic amines. Using an external nitrogen ligand, an enantioselective version, by desymmetrization of enantiotopic methyl-groups could be envisioned. On the other hand, Cramer and coworkers disclosed the asymmetric synthesis of β-lactams from α-chloroamides[161] by intramolecular C(sp^3)–H alkylation in the presence of a chiral ligand[65]. In this remarkable work, they were for the first time able to both build a monocyclic ring system and to construct a C(sp^3)–C(sp^3) bond under Pd^{0}-catalyzed C(sp^3)–H activation. Whereas impressive levels of enantioselectivity were obtained, this methodology is limited to the functionalization of activated secondary C-H bonds adjacent to a (hetero)aryl or ester group (Scheme 72).



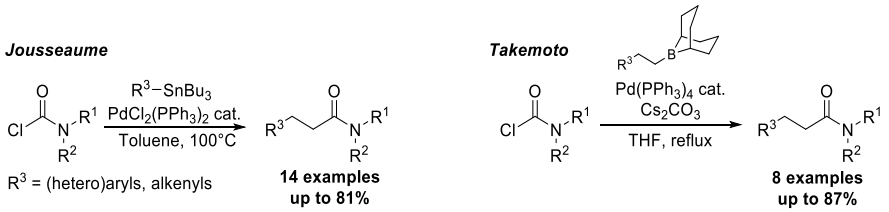
Scheme 72 : *Synthesis of β-lactams by Pd^{II} and Pd^{0} –catalyzed C(sp^3)–H activation*

Recently, we were able to obtain β-lactams in moderate yields (*Table 8*), thus inspiring us to develop a more practical route to this moiety. Thanks to literature elements, we envisioned to use carbamoyl chlorides for the synthesis of β-lactams by Pd(0)-Catalyzed C(sp^3) activation.

3. Carbamoyl chlorides in transition metal-catalysis

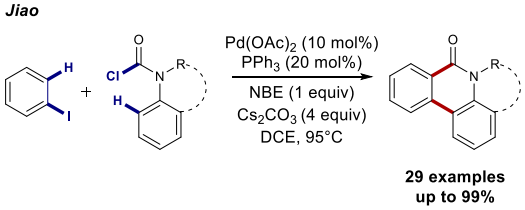
3.1. Intermolecular processes

The first efficient application of carbamoyl chlorides in catalysis was achieved in the field of cross-coupling. Indeed, using organotin reagents, Jousseaume and coworkers described an easy entry to amide synthesis via palladium-catalyzed cross-coupling reactions[162]. Few years later, this approach was extended to Suzuki cross-couplings thanks to a one-pot amidation of olefins through the palladium-catalyzed coupling of alkylboranes and carbamoyl chlorides[163] (Scheme 73).



Scheme 73 : *Carbamoyl chlorides in cross-coupling reactions*

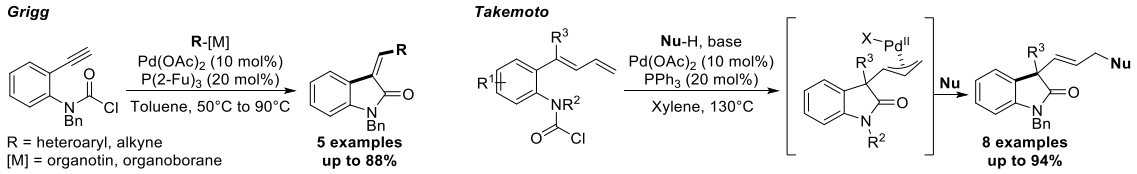
Recently, Jiao and coworkers reported a new synthesis of phenanthridinones taking advantage of the Pd/norbornene (NBE) chemistry developed by Catelani and coworkers[164]. Thanks to dual C-H bond activation, they have described an efficient synthesis of phenanthridinones, starting from readily available aryl iodides and carbamic chlorides[165] (Scheme 74).



Scheme 74 : *Synthesis of phenanthridinones via intermolecular dehydrogenative annulation*

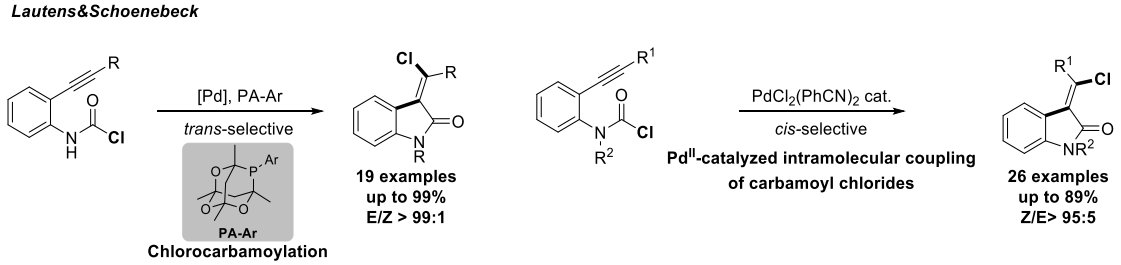
3.2. Intramolecular processes

Whereas reported classical intramolecular Heck processes (terminated via β-hydride elimination) were suffering from a lack of generality and efficiency[115a, 166], Grigg and coworkers described the synthesis of oxindoles via palladium-catalyzed Heck cyclization followed by a cross-coupling reaction using organotin or organoborane reagents. Based on the same initial palladium-catalyzed Heck cyclization and by trapping the *in situ* generated π-allylpalladium complex, Takemoto and coworkers reported a flexible synthesis of oxindoles[167] (Scheme 75).



Scheme 75 : *Access to oxindole derivatives via sequential carbopalladation/functionalization*

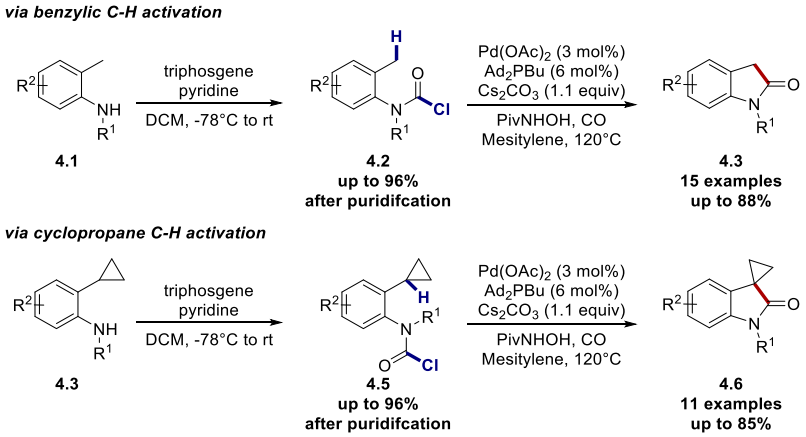
On the other hand, carbamoyl chlorides can be used for the carbohalogenation of unsaturated C-C bonds. Based on the initial reports of Tong and coworkers[168], Lautens and Schoenebeck turned their attention to develop an efficient and stereoselective synthesis of methylene oxindoles which are valuable intermediates to access biologically active compounds (Scheme 76).



Scheme 76 : *Stereoselective synthesis of methylene oxindoles*

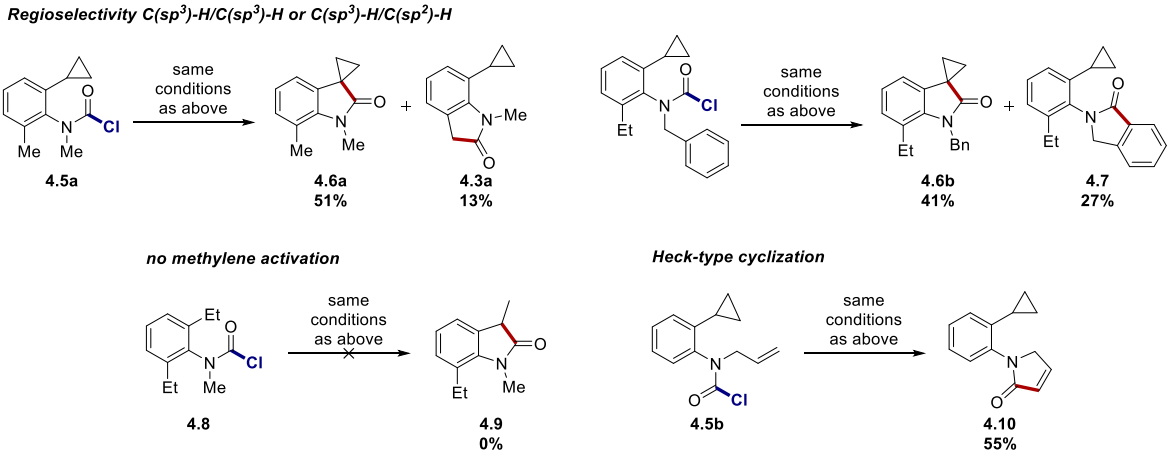
3.3. Palladium(0)-Catalyzed Carbamoylation of activated C(sp^3) bonds

During the course of their researches, Takemoto and coworkers exploited the use of readily accessible and relatively stable carbamoyl chlorides in palladium-catalyzed reactions. They envisioned to take advantage of carbamoyl chlorides to develop a new concise route to oxindoles via C-H activation. Starting from readily available secondary amines **4.1&4.3**, they obtained the corresponding carbamoyl chlorides **4.2&4.5** in high yield after purification. After optimization of the reaction conditions, they completed a broad scope for the synthesis of oxindoles **4.3** and spiro-oxindoles **4.6**, thanks to the functionalization of activated benzylic and cyclopropane C-H bonds (Scheme 77).



Scheme 77 : *Scope of the Palladium(0)-Catalyzed C(sp^3)-H Carbamoylation*

Of note, during the study of the reaction scope, they observed preferential activation of cyclopropane C-H bonds leading to compounds **4.6a&4.6b** over benzylic or aromatic C-H bonds leading to **4.3a** and **4.7** respectively. This highlights the special character of such strained hydrocarbons[169]. Indeed, they are easier to activate due to their special bonding properties and hybridization despite their higher pK_a-value (46) compared to benzylic (41) or aromatic (43) C-H bonds. Moreover, challenging methylene C-H activation does not occur in this methodology. Finally, when the alkene derivative **4.5b** is engaged under the optimized conditions, exclusive carbopalladation was observed leading to γ-lactams **4.10** (Scheme 78).

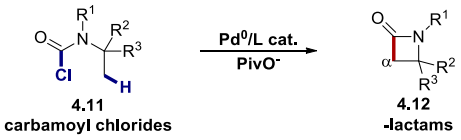


Scheme 78 : *Regioselectivity and reactivity issues*

4. Synthesis of β-Lactams by Palladium(0)-Catalyzed C(sp^3)-Carbamoylation

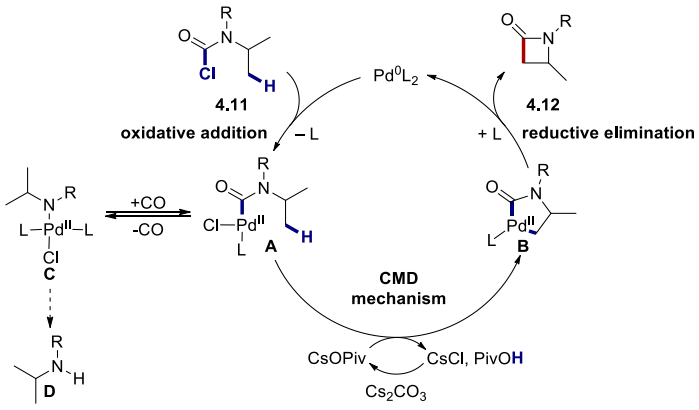
4.1. Optimization of the reaction

Inspired by these seminal reports, we envisioned to access β-lactams efficiently, thanks to the construction of the C(O)-C_α bond through Pd(0)-catalyzed C(sp^3)-H carbamoylation (Scheme 79).



Scheme 79 : *Transformation envisioned*

Before beginning the optimization, we considered the mechanism of the reaction. The accepted catalytic cycle for this transformation starts with the oxidative addition of a monoligated Pd(0) complex into the acyl chloride bond of **4.11**. At this stage, instead of the classical ligand exchange (with pivalate base for example), followed by the CMD mechanism leading to intermediate **B** and the desired product after reductive elimination, a competitive decarbonylation leading to the undesired intermediate **C** could occur. This latter can lead either to the free amine **D** or to the competent acyl palladium complex **A** after reinsertion of the carbon monoxide. At the outset of this study, we could not exclude the reversibility of this step (**A↔C**). Nevertheless, we were aware that this competitive decarbonylation could impact the reaction course (Scheme 80).



Scheme 80 : *Simplified mechanism*

In line with our previously described methodology, we designed the substrate **4.11a** for the optimization in order to obtain valuable compounds after C-H activation. Indeed, removal of the TMB group should deliver the corresponding free-*NH*-lactam which would be useful to access interesting compounds such as aztreonam or tigemonam through sulfatation (Figure 10).

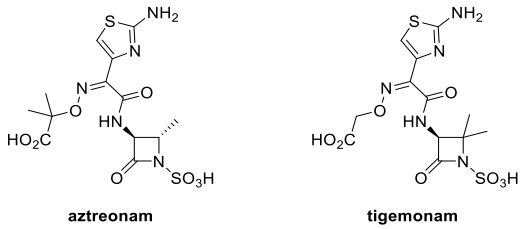
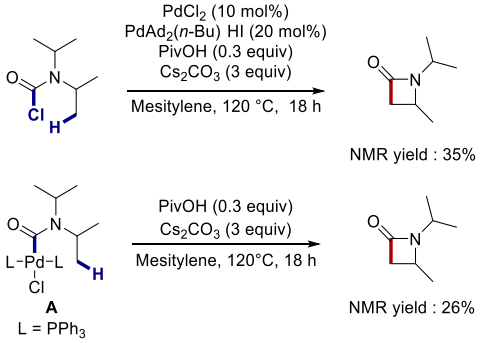


Figure 10 : *Available targets thanks to access to free-NH-lactams*

Initially, we conducted the optimization with $Pd(PPh_3)_4$ as catalyst and cesium pivalate as the active base in various solvents (entries 1-6). We were pleased to find that the desired β-lactam **4.12a** was obtained in moderate yield (entries1-2;5-6), thereby confirming the feasibility of this transformation. After variation of different parameters without any improvement, we decided to use a CO atmosphere to limit the formation of undesired amine **4.13a** and/or urea **4.14a** side-products. Surprisingly, using the same catalytic system under an atmosphere of CO, the reaction was negatively impacted providing only low yield for the desired product **4.13a** (entries 7-8). Visually, formation of Pd black was clearly observed immediately after the addition of CO. Gratifyingly, we found out that the electron-rich and sterically demanding $PAd_2(n\text{-Bu})$ phosphine (CataCXium A) was crucial to suppress this catalyst deactivation (entry 9) which is in agreement with observations of Beller and coworkers during their work on the formylation of aryl bromides[170] as well as the catalytic system of Takemoto [50-51, 69]. After variation of different parameters such as the palladium source (entries 9-15), equivalents of base (entry 16), solvent (entry 17) and temperature (entries 18-19), we have identified the optimal catalytic system for this transformation allowing the isolation of **4.12a** in 85% yield (entry 17). Different ligands (entries 20-24) and the structurally close di(1-adamantyl)benzylphosphine ligand (entry 25) were found to be less efficient. Employing the third generation of Buchwald's precatalyst and the Pd(0)-L_2 complex with the cataCXium A ligand allows to obtain the desired product **4.12a** with similar efficiency (entries 26-27). In addition, we were able to isolate the oxidative addition complex **A** (R = *i*-Pr, L = PPh_3) following Gaunt's procedure[160]. Submitting this latter to our optimized conditions allowed the formation of the corresponding β-lactam with comparable efficiency than the classical

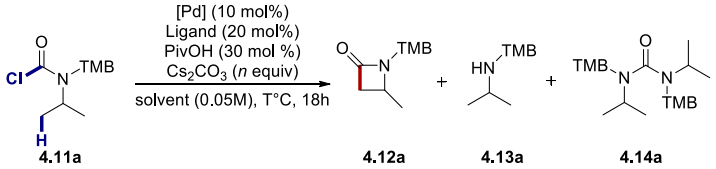
reaction with the carbamoyl chloride (Scheme 81). These experiments confirm that the complex **A** is a competent intermediate and support the Pd^0-Pd^{II}-Pd^0 mechanism depicted in Scheme 80.



Scheme 81 : *Control experiments validating the Pd^0-Pd^{II}-Pd^0 mechanism*

Starting from amine **4.13a** instead of carbamoyl chloride **4.11a**, no trace of the β-lactam **4.12a** was observed(entry 28), thereby confirming that our system differs from the Pd^{II}-Pd^0-Pd^{II} developed by Gaunt and coworkers[160]. Interestingly, in absence of CO, the current catalytic system is still competent for the formation of β-lactam **4.12a**, however with a slightly decreased yield (-22%) (entry 29). At this stage, we were looking to develop a more convenient protocol. Even if CO is an abundant chemical feedstock and is widely used in various industrial processes, a special safety equipment has to be used due to its toxicity. In order to develop a more user-friendly methodology, we turned our attention to the use of non-gaseous source of stoichiometric CO. Unfortunately, different sources of CO already competent in carbonylative methodologies such as the triruthenium dodecacarbonyl [171], paraformaldehyde[172], trimethylacetic formic anhydride[173] were found to be inneficient. Then, we envisioned to use the two-chamber (COware) system developed by Skrydstrup and coworkers[174]. Gratifyingly, the use of this two-chamber system allows the restoration of the reactivity (entries 30-31). Of note, when 3 equivalents of COgen were used, the reaction proceeds with higher efficiency (92%, entry 31) compared to the use of an excess of CO (85%, entry 17). Moreover, the reaction can be scaled up tenfold without loss of the efficiency (95%, entry 32). Finally, we were pleased to find that the reaction can proceed nicely when the experiment was set up with technical-grade solvent without any precaution (75%, entry 33), thereby providing a robust and user-friendly methodology (*Table 9*).

Table 9 : *Selected conditions of the optimization*

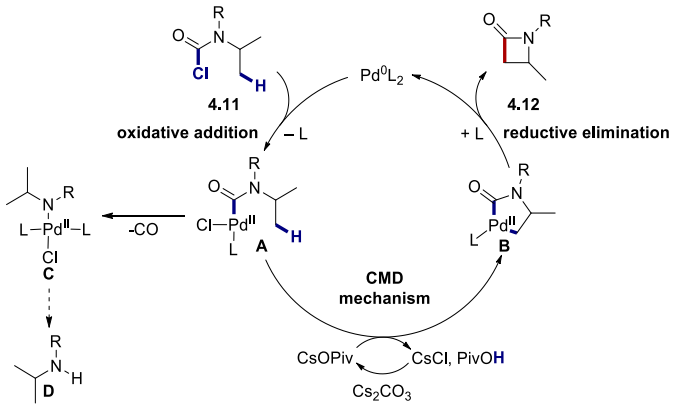


Entry	[Pd]	Ligand	n	Solvent	CO source		Temp [°C]	Yield **4.12a** [%][c]
					balloon	COgen[b] (equiv)		
1	$Pd(PPh_3)_4$	–	1.5	THF	-	-	120	45%
2	$Pd(PPh_3)_4$	–	1.5	DME	-	-	120	37%
3	$Pd(PPh_3)_4$	–	1.5	DMF	-	-	120	0%
4	$Pd(PPh_3)_4$	–	1.5	DMSO	-	-	120	0%
5	$Pd(PPh_3)_4$	–	1.5	Toluene	-	-	120	45%
6	$Pd(PPh_3)_4$	–	1.5	Xylene	-	-	120	47%
7	$Pd(PPh_3)_4$	–	1.5	Xylene	✓		120	27%
8	$Pd(OAc)_2$	PPh_3	1.5	Xylene	✓		120	10%
9	$Pd(OAc)_2$	$PAd_2(n\text{-Bu})\bullet HI$	1.5	Xylene	✓		120	45%
10	$Pd(OPiv)_2$	$PAd_2(n\text{-Bu})\bullet HI$	1.5	Xylene	✓		120	62%
11	$Pd_2(dba)_3$	$PAd_2(n\text{-Bu})\bullet HI$	1.5	Xylene	✓		120	42%
12	$Pd(MeCN)_4\bullet HBF_4$	$PAd_2(n\text{-Bu})\bullet HI$	1.5	Xylene	✓		120	35%
13	$Pd(MeCN)_2Cl_2$	$PAd_2(n\text{-Bu})\bullet HI$	1.5	Xylene	✓		120	64%
14	$PdMe_2(TMEDA)$	$PAd_2(n\text{-Bu})\bullet HI$	1.5	Xylene	✓		120	66%
15	$PdCl_2$	$PAd_2(n\text{-Bu})\bullet HI$	1.5	Xylene	✓		120	76%
16	$PdCl_2$	$PAd_2(n\text{-Bu})\bullet HI$	3	Xylene	✓		120	82%
17	$PdCl_2$	$PAd_2(n\text{-Bu})\bullet HI$	3	Mesitylene	✓		120	92% (85%)
18	$PdCl_2$	$PAd_2(n\text{-Bu})\bullet HI$	3	Mesitylene	✓		110	57%
19	$PdCl_2$	$PAd_2(n\text{-Bu})\bullet HI$	3	Mesitylene	✓		130	58%
20	$PdCl_2$	$P(o\text{-tol})_3$	3	Mesitylene	✓		120	15%
21	$PdCl_2$	PPh_3	3	Mesitylene	✓		120	24%
22	$PdCl_2$	PCy_2Ph	3	Mesitylene	✓		120	41%
23	$PdCl_2$	$PtBu_3\bullet HBF_4$	3	Mesitylene	✓		120	21%
24	$PdCl_2$	$PCy_3\bullet HBF_4$	3	Mesitylene	✓		120	28%
25	$PdCl_2$	PAd_2Bn	3	Mesitylene	✓		120	18%
26	$PAd_2(n\text{-Bu})\text{-Pd-G3}$	–	3	Mesitylene	✓		120	80%
27	$Pd[PAd_2(n\text{-Bu})]_2$	–	3	Mesitylene	✓		120	88% (85%)
28[d]	$PdCl_2$	$PAd_2(n\text{-Bu})\bullet HI$	3	Mesitylene	✓		120	0%
29	$PdCl_2$	$PAd_2(n\text{-Bu})\bullet HI$	3	Mesitylene	–	–	120	70%
30	$PdCl_2$	$PAd_2(n\text{-Bu})\bullet HI$	3	Mesitylene		✓ (1.5)	120	75%
31	$PdCl_2$	$PAd_2(n\text{-Bu})\bullet HI$	3	Mesitylene		✓ (3)	120	94% (92%)
32[e]	$PdCl_2$	$PAd_2(n\text{-Bu})\bullet HI$	3	Mesitylene		✓ (3)	120	(95%)
33[e]	$PdCl_2$	$PAd_2(n\text{-Bu})\bullet HI$	3	Mesitylene		✓ (3)	120	(75%)[f]

[a]Performed using 0.133 mmol of **1a** unless otherwise stated. [b]9-Methylfluorene-9-carbonyl chloride (COgen), $Pd(OAc)_2/P(t\text{-Bu})_3\bullet HBF_4$ cat., Cy_2NMe, mesitylene, two-chamber system (COware), both reaction chambers were placed at the same temperature. [c]Determined by NMR analysis using trichloroethylene as internal standard. Yield of isolated product **4.12a** is given within parentheses. [d]Using amine **4.13a** instead of **4.11a**. [e]Performed using 1.33 mmol (400 mg) of **4.11a** . [f]Performed using technical-grade mesitylene under non-inert conditions.

At this stage, we used the isotopically labelled ^{13}COgen to study the reversibility of the CO 1,1-deinsertion/1,1-reinsertion step (**A↔C**) depicted in Scheme 80. When the reaction was performed with this labelled ^{13}COgen, very slight ^{13}C incorporation was observed (2.5%). Thanks to this control experiment, we can suggest that the role of the CO

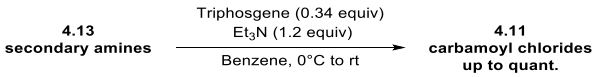
consists in saturating the reaction medium to limit the decarbonylation of intermediate **A**, thereby providing the mechanism shown below (Scheme 82).



Scheme 82 : *Revised mechanism*

4.2. Scope and limitations of the β-lactams synthesis

With the optimal conditions in our hands, we turned our attention to the scope and limitations of this methodology. To this purpose, more than 45 secondary amines **4.13** and 50 carbamoyl chlorides **4.11** were synthetized. For the amine synthesis, we mainly used three different methods of reductive amination as well as Michael type reactions. All the related data can be found in the experimental part. In the case of carbamoyl chloride synthesis, employing classical conditions, we were pleased to obtain a series of carbamoyl chlorides in high yield without any purification, thus giving us a rapid access to the precursors of C-H activation (Scheme 83).

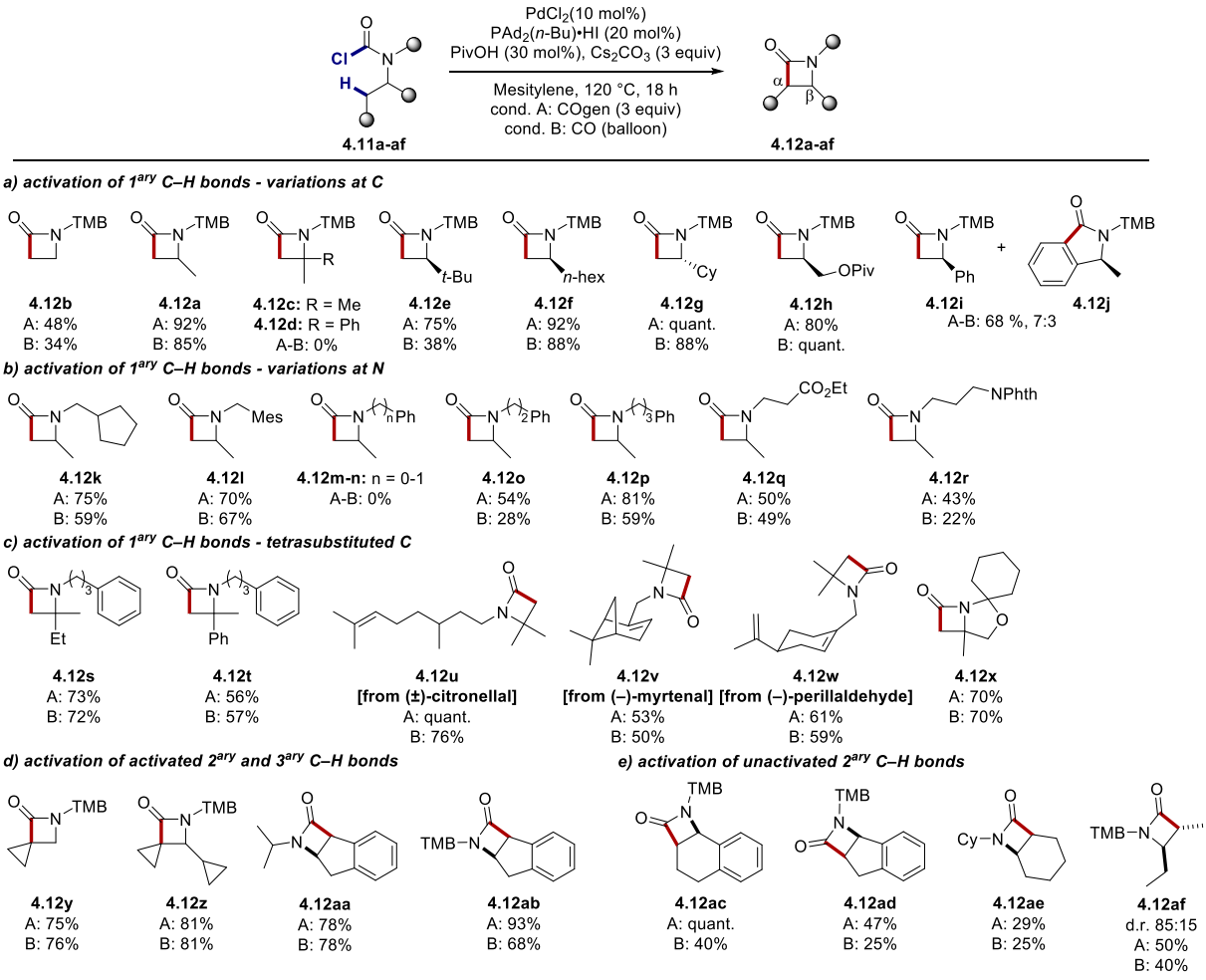


Scheme 83 : *Conditions for the synthesis of carbamoyl chlorides **4.11***

For comparison, for each substrate, we set up a reaction under both conditions. Importantly, in agreement with the optimization, the COgen conditions deliver in almost all cases the β-lactams with equal or higher efficiency compared to CO-balloon conditions. In addition, we were pleased to find that for several examples, such as **4.12e**, **4.12o-p**, **4.12r-u** and **4.12ab-ad**, the COgen could increase the yields from more than 20% yield, thereby highlighting the efficiency of this COgen-mediated reaction. We first examined the activation of primary C-H bonds with TMB-protected substrates **4.11a-i**, which can potentially deliver the free-*NH*-β-lactam after deprotection of the TMB group. Of note, the reaction proceeds decently with reactant **4.11b** bearing a disubstituted β-position, which is somewhat surprising.

Indeed, this latter does not benefit from Thorpe-Ingold and stastistic effects. This may point out the high reactivity of such intermediates in C-H activation. In line with this result, the reactions with reactants **4.11e-i** bearing a trisubstituted β-position give excellent yields, including the formation of chiral β-lactams **4.12e-12h** (obtained from the enantiopure secondary amines). Of note, when the substrate **4.11i** is submitted to the optimized conditions, a mixture of β-lactam **4.12i** and oxindole **4.12j** arising from the competition between C(sp^3)-H and C(sp^2)-H activation was observed. Interestingly, the β-lactam **4.12i** was preferentially formed, thereby reflecting the higher reactivity of the kinetically favorable 5-membered palladacycle intermediate in C-H activation. Surprisingly, potentially due to excessive repulsion between the TMB group and the β-tetrasubstitution of compounds **4.11c-d**, the reaction only proceeds through the decarbonylative pathway providing the undesired amine **4.13c-d** and/or urea **4.14c-d** side-products. We next investigated the nature of the *N*-substituent. Whereas, the reaction occurred in acceptable yields with different substitution patterns **4.12k**, **4.12l**, **4.12o-p** including functional groups such as ester **4.12q** and a protected amine **4.12r**, the reaction failed to deliver products **4.12m-n**. We assume that this is due to competitive C(sp^2)-H activation which leads to the formation of an unreactive palladacycle intermediate. Indeed, when the aryl moieties of precursors of C-H activation are substituted in ortho position, as it is the case for compounds **4.11a** and **4.11l**, no C(sp^2)-H activation can occur and the desired β–lactams **4.12a** and **4.12l** were obtained in good yield. Then, we turned our attention to reactants bearing a tetrasubstituted β-position. Whereas substrates **4.11c-d** were inefficient due to an excessive steric repulsion, less-hindered *N*-substituted compounds **4.12k-l** allow the formation of the corresponding β–lactams in good yield. Interestingly, β–lactams **4.12u-w** derived from the acyclic and cyclic monoterpenes were prepared in good yield allowing introduction of alkenes in this methodology. Noteworthy, no competitive C(sp^2)-H or carbopalladation was observed contrary

to the previous report of Takemoto (Scheme 78). Finally, the fused β–lactam **4.12x** was obtained in good yield, thus furnishing potential entry to bicyclic antibiotic derivatives. In addition to the activation of primary C-H bonds, nonconventional spirocyclic **4.12y-z** and fused β-lactams **4.12aa-ab** were synthetized thanks to the activation of activated secondary and tertiary C-H bonds. Gratifyingly, we were pleased to find that the activation of less-activated methylene C-H bonds can occur, thus furnishing compounds **4.12ac-af** with variable efficiency. Interestingly, the β-lactam **4.12ac** was obtained quantitatively, thereby demonstrating the efficiency of this methodology and should pave the way for further developments (Scheme 84).



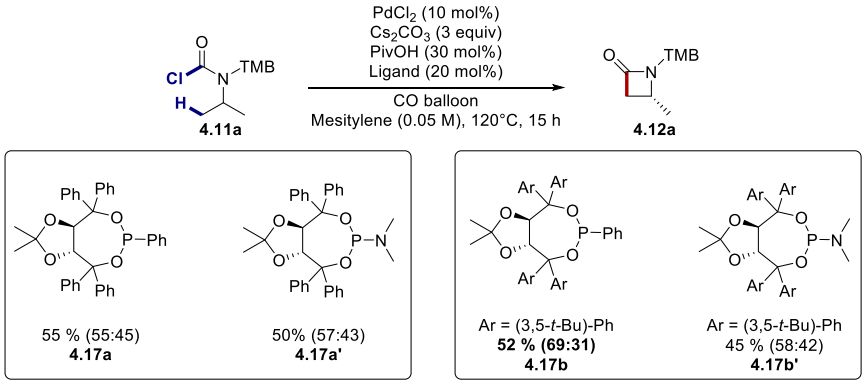
Scheme 84 : *Scope and limitations of the reaction*

4.3. Development of an enantioselective version

4.3.1. Initial results

As mentioned in paragraph 4.2.5 of Chapter 1, enantiodiscrimination in Pd(0)-catalyzed C(sp^3)-H activation can be achieved thanks to a chiral ancillary ligand or a chiral base. Taking advantage of previous reports, we first tried to identify a family of chiral ligands allowing reactivity as well as enantioinduction. After having tested various chiral NHCs, chiral binepines, chiral BINOL-derived phosphoramidites and phosphonites, we were pleased to find that chiral TADDOL-derived ligands seemed to be promising sources of chirality[62]. Indeed, whereas other chiral ligands only afforded low enantiomeric excess and low conversion, chiral TADDOL-derived ligands allowed to obtain partial conversion with low to moderate enantioinduction. Especially, identical reactivity and induction were observed between the phosphonite ligand **4.17a** and the phosphoramidite ligand **4.17a'**, modification of the aryl

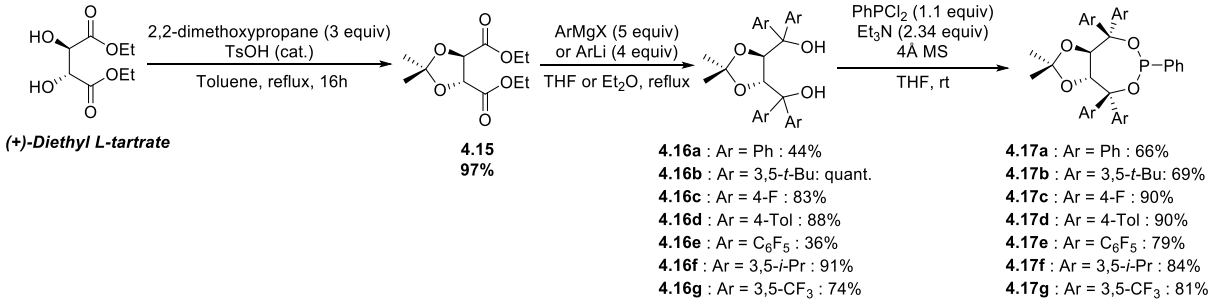
substituents of the phosphonite ligand affects significantly the enantioselectivity (**4.17** versus **4.17a**) (Scheme 85). However, phosphoramidites **4.17a'** and **4.17b'** provided the same selectivity. In order to improve the enantioselectivity, we thus turned our attention to modulate the electronic and steric properties of these chiral TADDOL-derived phosphonites thanks to the modification of the aryl substituents, the ketal moiety and the aryl part at the phosphorus atom.



Scheme 85 : *Inital results – Phosphonites versus Phosphoramidites*

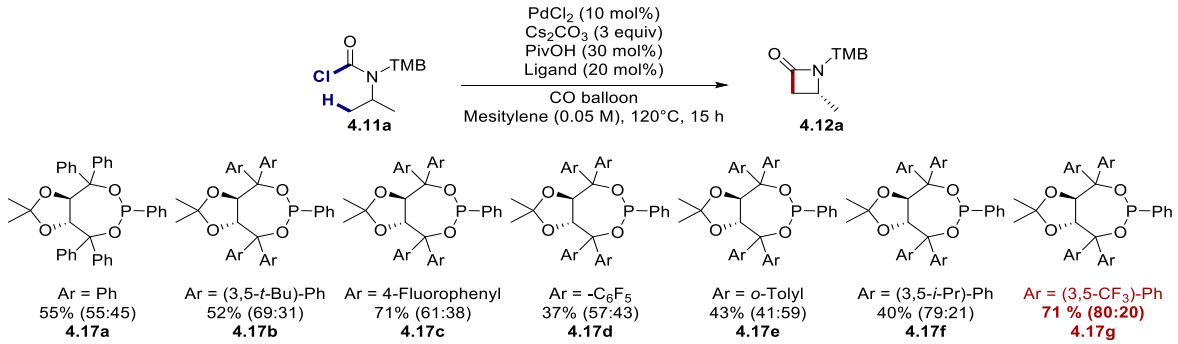
4.3.2. Synthesis of TADDOL-derived phosphonites and optimization of the reaction

In order to identify the best TADDOL-derived phosphonite, we decided to synthetize a series of ligands with modification of the aryl substituents next to the tertiary hydroxyl group. Since the initial report of Seebach and coworkers on the synthesis of TADDOL-derived phosphorus(III) ligands[175], the seminal synthetic approach was subjected to only slight improvements. Starting from the readily available (+)-Diethyl L-tartrate, a two-step sequence involving the protection of the diol and nucleophilic addition of organometallic species allows the obtention of TADDOLs **4.16a-g**. Thanks to this synthetic route, the reaction of TADDOLs **4.16a-g** with the commercially available *P*,*P*-Dichlorophenylphosphine allows the synthesis of a first batch of seven TADDOL-derived phosphonites **4.17a-g** (Scheme 86).



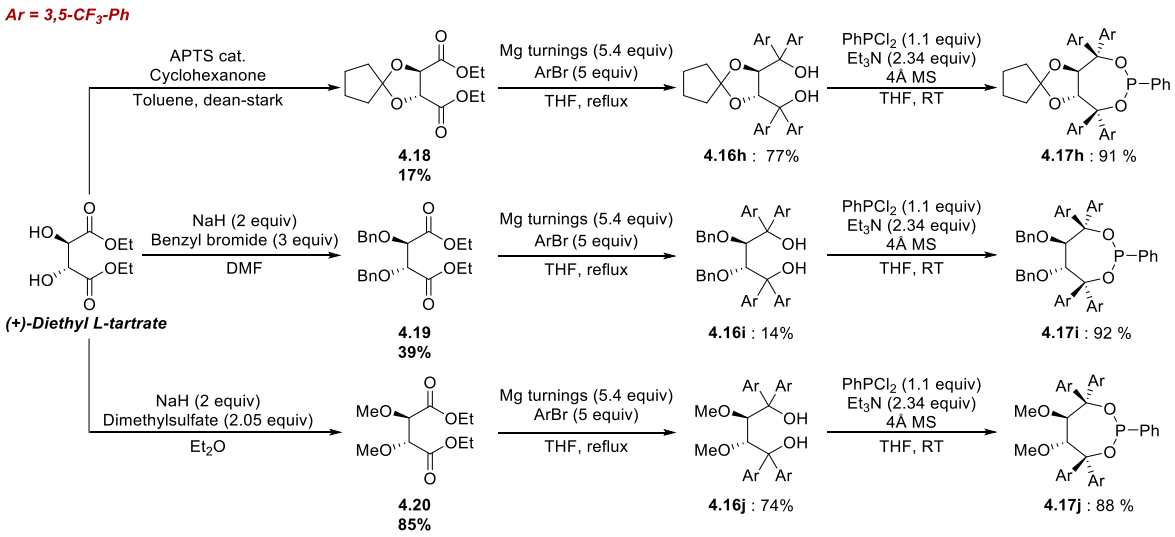
Scheme 86 : *Synthesis of TADDOL-derived phosphonites **4.17a-g***

We then tested these different ligands under the optimized racemic conditions. Whereas ligands **4.17c-e** were less efficient in term of enantiomeric excess compared to the initial result with ligand **4.17b**, we were pleased to find that ligands with a 3,5-disubstituted aryl pattern **4.17f-g** furnished higher enantioselectivity values compared to the others. Especially, ligand **4.17g** was the most promising in terms of reactivity and enantioselectivity. We thus decided to continue the optimization with this 3,5-bis(trifluoromethyl)phenyl pattern (Scheme 87).



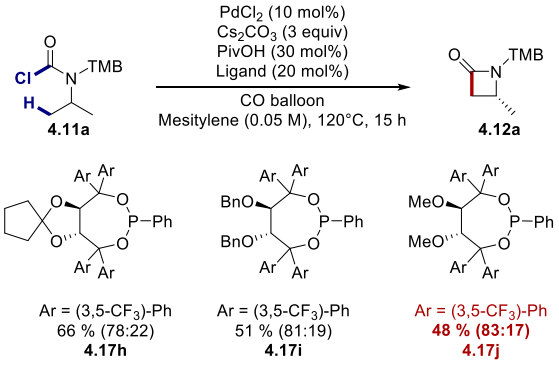
Scheme 87 : *Influence of the aryl moiety on the enantioselectivity and reactivity*

We next turned our attention to the modification of the backbone of ligand **4.17g**. For this purpose, we synthetized three new TADDOL-derived phosphonites **4.17h-j** using classical conditions (Scheme 88).



Scheme 88 : *Synthesis of backbone-modified ligands **4.17h-j***

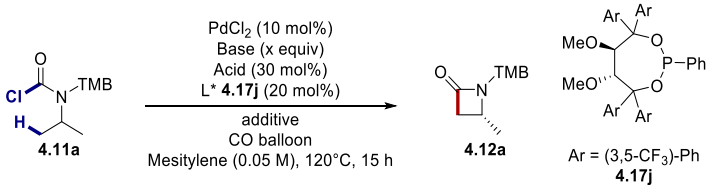
Whereas ligand **4.17h** bearing a cyclopentanonide resulted in slightly decreased reactivity and enantioselectivity, we were pleased to find that TADDOL **4.17i** and **4.17j** with acyclic backbones positively affected the enantioselectivity. Unfortunately, both TADDOL **4.17i** and **4.17j** afforded lower yields than ligand **4.17g** (Scheme 89).



Scheme 89 : *Influence of the backbone moiety on enantioselectivity and reactivity*

At this stage, a slight optimization was performed using TADDOL ligand **4.17j**. After having tested various other bases and acids (entries 4-7) as well as an additive (entry 3) without any improvement, higher reactivity was recovered using 1.5 instead of 3 equivalents of cesium carbonate (entry 1).

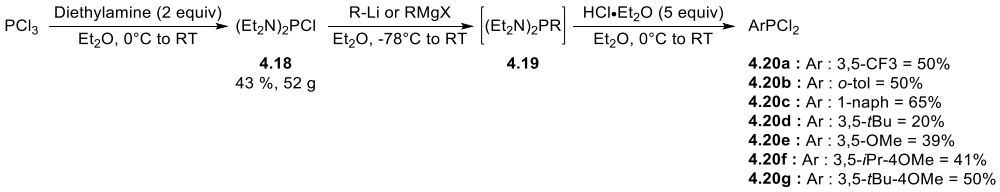
Table 10 : *Optimization of the reaction conditions*



Entry	Base (x equiv)	Acid	Additive	Yield %[a]	e.r.
1	Cs_2CO_3 (1.5 equiv)	PivOH	-	63	83:17
2	Cs_2CO_3 (1.1 equiv)	PivOH	-	46	83:17
3	Cs_2CO_3 (3 equiv)	PivOH	4Å MS	23	84:16
4	K_2CO_3 (3 equiv)	PivOH	-	23	83:17
5	Rb_2CO_3 (3 equiv)	PivOH	-	49	83:17
6	K_3PO_4 (3 equiv)	PivOH	-	29	84:16
7	Cs_2CO_3 (3 equiv)	PivNHOH	-	53	82:18

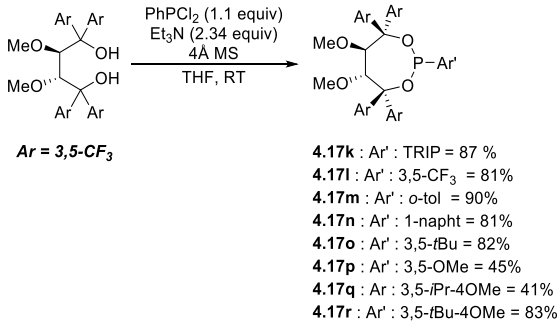
[a] *Yield of isolated product* ***4.12a***

After having modulated the steric bulk of our TADDOL ligands with variations of the backbone and aryl substituents, we turned our attention to tune both electronic and steric properties by introducing substituents on the aryl moiety at the phosphorus atom. To this purpose, we synthetized seven *P,P*-Dichloroarylphosphines **4.20a-g** through the reaction of an organolithium or organomagnesium with the Bis(diethylamino)chlorophosphine **4.18** followed by an acidic treatment. Of note, this protocol allows to obtain the monosubstituted chlorophosphines **4.20a-g** in an efficient manner by avoiding over-addition by-products often observed when organolithiums or organomagnesiums are reacted with phosphorus trichloride (Scheme 90).



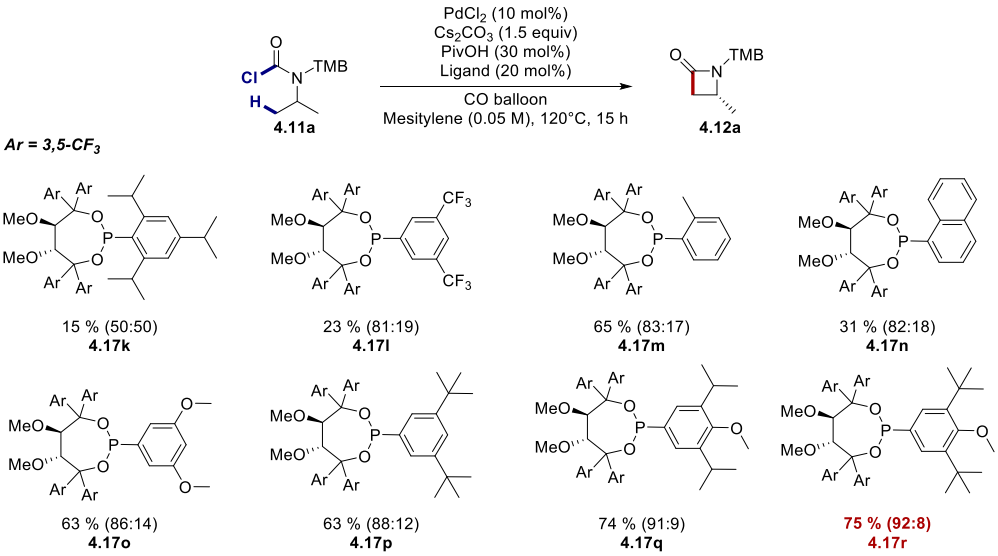
Scheme 90 : *Synthesis of dichloroarylphosphines* ***4.20a-g***

Thanks to the synthesis of these *P*,*P*-Dichloroarylphosphines **4.20a-g**, we were able to obtain eight new TADDOL-derived phosphonites **4.17k-r** in good yield with different aryls at the phosphorus atom (Scheme 91).



Scheme 91 : *Synthesis of TADDOL-derived phosphonites* ***4.17h-o***

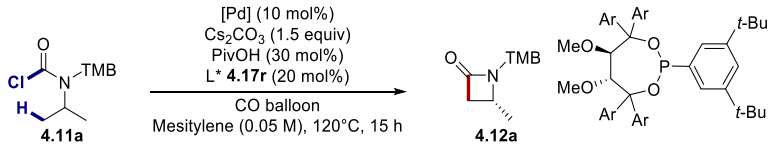
We tested the new ligands **4.17k-r** under the new optimized conditions. Ligand **4.17k** was found to inhibit the catalytic system. We assume that the important steric bulk induced by the TRIP moiety hinders coordination of the phosphonite to the metal center. Consequently, only the background reaction occurs, thereby explaining the racemic product and the low yield obtained (Scheme 92). In the case of ligands **4.17l-n**, no improvement was observed. Interestingly, electron-withdrawing groups on the ligand **4.17l** clearly reduce the efficiency of the reaction, whereas electron-donating groups present in **4.17o** and **4.17q-r** positively affect the reaction. Of note, a 3,5-disubstitution pattern with a bulky group such as *tert*-butyl moiety (**4.17q**) increases the enantioinduction. Finally, we were pleased to find that a 3,5-disubstitution pattern with a methoxy group at the para position significantly improves both yield and enantioselectivity. At this stage, we decided to stop the ligand synthesis for this enantioselective version due to a lack of time. In order to rationalize the effect of the modification of the aryls substituents, the ketal moiety and the aryl part at the phosphorus atom, it would be interesting to characterize the steric and electronic properties of ligands **4.17a-r**.



Scheme 92 : *Influence of the aryl at the phosphorus atom on enantioselectivity and reactivity*

In parallel to the synthesis of these new ligands (**4.17k-r**), we optimized other parameters such as the palladium source and the solvent of the reaction. We first examined palladium sources (Table 11). In all cases, the reaction proceeded with similar efficiency using either Pd(0) or Pd(II) precatalysts. However, a slight fluctuation of the enantioselectivity was observed (entries 1-7), thus leading us to continue with $PdCl_2$ or $Pd(MeCN)Cl_2$.

Table 11 : *Selected source of palladium*



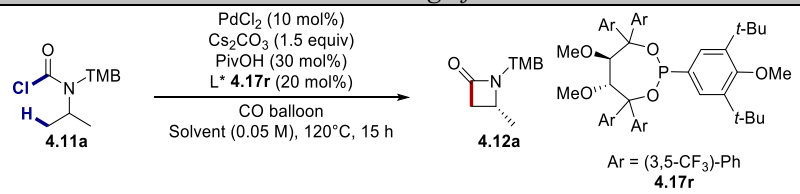
Entry	[Pd]	Yield %[a]	e.r.
1	$Pd(dba_2)$	68	83:17
2	$Pd(MeCN)_2Cl_2$	68	88:12
3	$Pd(OPiv)_2$	74	85:15
4	$Pd(TFA)_2$	57	83:17
5	$Pd(Me)_2TMEDA$	68	86:14
6	$Pd(COD)(Me)_2$	60	86:14
7	$PdCl_2$	63	88:12

[a] *Yield of isolated product* ***4.12a***

We next investigated the influence of the solvent on both reaction efficiency and enantioselectivity (Table 12). Whereas non-aromatic polar aprotic solvents such as DMAc completely shut down the reaction (entry 1), aromatic solvents allow the formation of the desired product. Unfortunately, among all tested solvents (entries 2-14), mesitylene was found to be the most efficient. Despite all these optimizations, only an acceptable e.e. of 84% for the

desired product **4.12a** was obtained. Nevertheless, this result represents an unprecedented example of desymmetrization of unactivated methyl groups[65].

Table 12 : *Screening of the solvent*

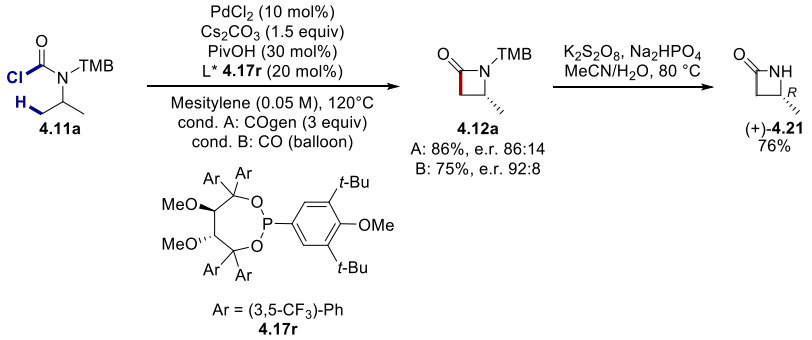


Entry	solvent	Yield %[a]	e.r.
1	DMAc	0	-
2	1,2,4-trimethylbenzene	60	81:19
3	Xylene (*o,m,p*)	71	86:14
4	*p*-xylene	69	86:14
5	*o*-xylene	71	87:13
6	*m*-xylene	46	85:15
7	Anisole	66	86:14
8	1,3-dimethoxybenzene	54	86:14
9	Chlorobenzene	51	88:12
10	Nitrobenzene	40	85:15
11	*p*-Cymene	63	86:14
12	Cumene	57	87:13
13	Benzonitrile	26	78:22
14	Mesitylene	75	92:8

[a] *Yield of isolated product* ***4.12a***

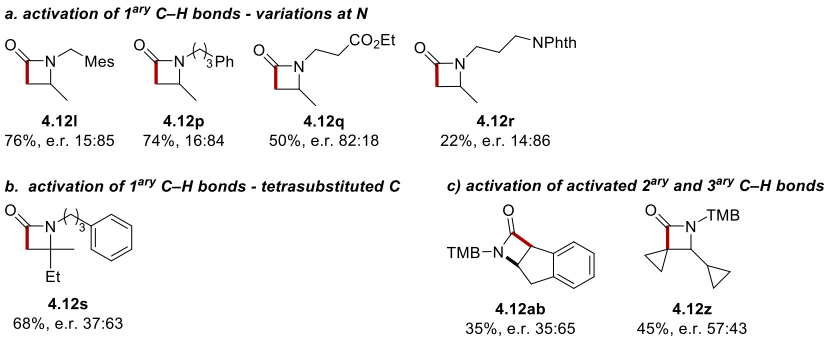
4.3.3. Scope of the enantioselective version

We next applied these optimized conditions to the same COware system as in the racemic version. As expected from previous results, a higher reactivity was observed using this system, furnishing compound **4.12a** in 86% yield. However, somewhat surprisingly, the enantioselectivity of the reaction was significantly decreased, thus leading us to use a CO balloon for the scope of the enantioselective version. Interestingly, after a slight optimization, the TMB group can be removed by oxidative cleavage employing potassium persulfate[176], thus providing the free lactam (*R*)-**4.21**. The absolute configuration was assigned considering the optical rotation of the enantiopure lactam, which was synthetized thanks to the separation of diastereoisomeric precursors[177].



Scheme 93 : *Enantioselective synthesis of β-lactams through the desymmetrization of methyl groups*

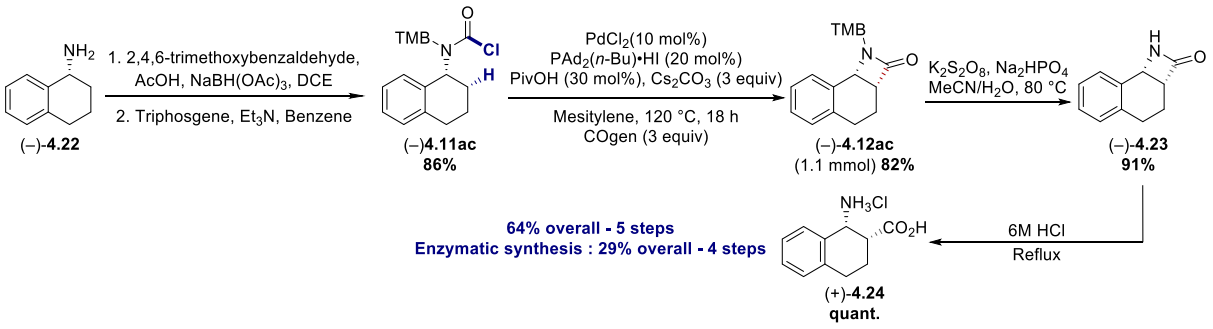
We next investigated the scope of this enantioselective version (Scheme 94). Whereas, the enantiomeric excess slightly decreases in the case of *N*-isopropyl compounds **4.12l-p-q-r**, almost no enantioinduction was observed for compound **4.12s** bearing a tetrasubstituted carbon. Analogous to the compound **4.12p**, steric hindrance brought by the tetrasubstituted carbon probably affects the enantiodetermining step. Finally, we investigated the possibility to activate methylene and methine C-H bonds of compounds **4.12ab** and **4.12z** under the optimized conditions for the activation of *N*-isopropyl C-H bonds. Unfortunately, as observed for compound **4.12s**, no enantioinduction was obtained. Moreover, the yield was moderate.



Scheme 94 : *Scope of the enantioselective version*

4.4. Application of the methodology

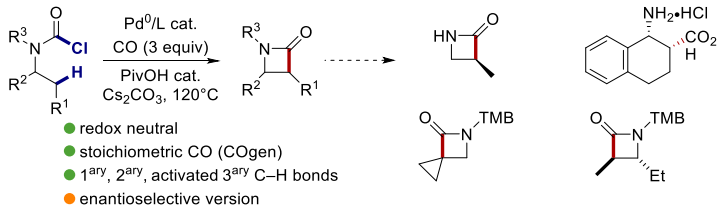
Finally, we sought to apply our methodology for the construction of valuable compounds. For this purpose, we turned our attention to the synthesis of the enantiopure β-aminoacid **4.24**, initially obtained by enzymatic resolution[178] and used for the construction of foldamers[179]. We envisioned taking advantage of our methodology (Scheme 84) to provide an efficient synthesis of (+)-**4.24**. Starting from the commercially available enantiopure tetrahydronaphthylamine **4.22**, the precursor of C-H activation (-)-**4.11ac** was prepared in 86% yield without purification. Then, we applied our optimized conditions to obtain the enantiopure tricyclic β-lactam (-)-**4.12ac** in good yield. Finally, removal of the TMB group under oxidative conditions and ring opening of the residual β-lactam (-)-**4.23** afforded the desired product in very good overall yield compared to the previous enzymatic synthesis, thereby highlighting the synthetic potential of C-H activation to reach valuable compounds in an efficient manner (Scheme 95).



Scheme 95 : *Synthesis of enantiopure β-aminoacid (+)-**4.24***

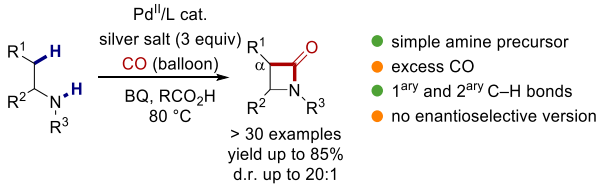
5. Conclusion

In summary, we have developed a new synthesis of β-lactams through Palladium(0)-catalyzed C(sp^3)-carbamoylation. Importantly, we described a user-friendly process using stoichiometric carbon monoxide in a two-chamber system allowing a good practicability and safe conditions. Starting from readily accessible carbamoyl chlorides, we were pleased to find that primary, secondary and activated tertiary C-H bonds were competent in this methodology, thereby furnishing a broad scope with different functional groups. Furthermore, interesting unconventional spirocyclic and fused β-lactams were obtained. Interestingly, an enantioselective version of this reaction was developed using a new TADDOL-derived phosphonite. Finally, application of this methodology allows to obtain valuable enantiopure free β-lactams and β-aminoacids in an efficient manner.



Scheme 96 : *Overview of our β-lactams synthesis*

During the writing of this manuscript, Gaunt and coworkers reported an impressive palladium(II)-catalyzed carbonylation of methylene C-H bonds from aliphatic amines allowing the synthesis of highly trans-disubstituted β-lactams[180].



Scheme 97 : *Activation of methylene C-H bonds by Gaunt and coworkers*

General conclusion

Over the past decade, the transition metal-catalyzed intramolecular activation of unactivated C-H bonds has emerged as a powerful method for organic chemists. Indeed, due to the ubiquity of C-H bonds, their direct and selective functionalization provides a rapid access to molecular complexity in an atom- and step-economical fashion. Within this field, my Ph.D thesis was centered on the total synthesis of marine natural products and bioactive compounds as well as the development of new methodologies based on palladium(0)-catalyzed C(sp^3)-H bond activation.

Recently, our group developed a straightforward access to hexahydroindoles by intramolecular C(sp^3)-H alkenylation. We first investigated the application of this new methodology in combination with a directed C(sp^3)-H arylation to achieve a collective synthesis of aeruginosins. Notably, we were able to scale-up the synthesis of aeruginosin 298A to obtain this latter in unprecedented yield and quantity. Moreover, we could achieve the first total synthesis of aeruginosins 98A and 98C thanks to a fine-tuning of the final hydrogenation step, which allowed limiting concomitant dehalogenation (Figure 11).

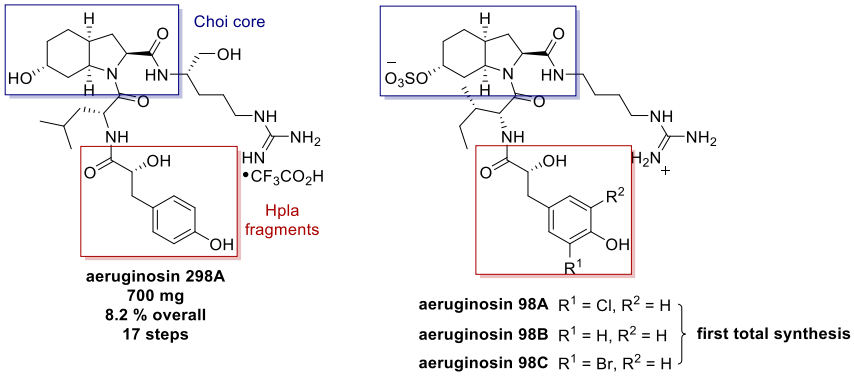
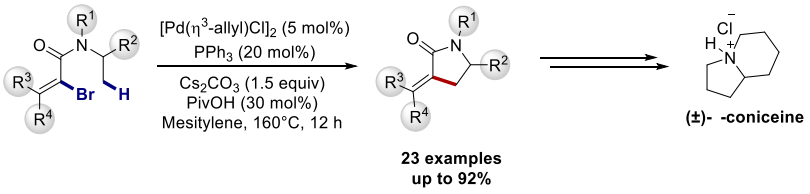


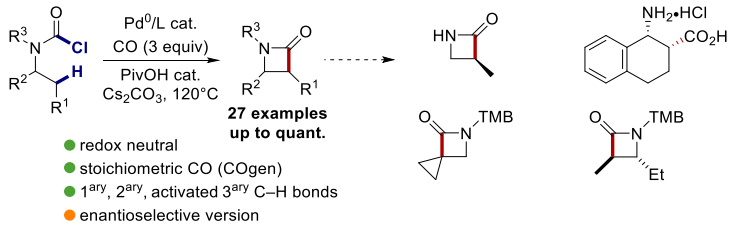
Figure 11 : *Collective synthesis of aeruginosins*

In the second part, we turned our attention to the development a new palladium(0)-catalyzed C(sp^3)-H alkenylation starting from easily available acyclic bromoalkenes. This new methodology allows to obtain a broad range of γ-lactams by modification of R^1-R^4 groups. Moreover, these lactams can be used as valuable building blocks as demonstrated by the synthesis of the indolizidine alkaloid (±)–δ–coniceine and of a plakoridine A precursor (Scheme 98).



Scheme 98 : *Overview of the α-alkylidene-γ-lactams synthesis via C(sp^3)-H alkenylation*

Finally, we developed a general and user-friendly synthesis of β-lactams using readily available starting materials. A broad scope including activation of primary, secondary, and activated tertiary C-H bonds was described, in contrast to previous methods based on C(sp^3)-H bond activation. In addition, an enantioselective version was enabled thanks to a TADDOL-derived phosphonite ligand. Moreover, these lactams can be used as valuable building blocks as demonstrated by the synthesis of enantiopure free β-lactams and β-aminoacids (Scheme 99)



Scheme 99 : *Overview of the synthesis of β-lactams via C(sp^3)−H Carbamoylation*

Experimental section

1. General information

Techniques: All reactions involving air-sensitive material were carried out in pre-dried glassware under an argon atmosphere by using Schlenk techniques employing double-line argon-vacuum lines and working in an argon-filled glove box. Analytical thin layer chromatography (TLC) was performed using pre-coated Merck silica gel 60 F254 plates (0.25 mm). Visualization of the developed chromatogram was performed by UV absorbance (254 nm) or TLC stains (KMnO4 and Phosphomolybdic acid). Flash chromatography was performed using Silicycle SiliaFlash P60 (230-400 mesh) with the indicated solvent system, using gradients of increasing polarity in most cases.

Chemicals:

Anhydrous solvents were obtained by distillation over calcium hydride (xylenes) or by distillation over sodium (mesitylene, toluene). Anhydrous THF, DME, DMF, DMSO, were purchased from Acros Organics. The solvents were degassed by three cycles of freeze-pump-thaw and storing in single-necked flasks equipped with a J-Young PTFE valve when necessary. PdCl2, Pd(OAc)2, Pd(PPh3)4 were purchased from Strem. All other chemical reagents were purchased from Sigma-Aldrich, Acros Organics, Fisher, Solvias and Fluorochem and used as received without further purification unless otherwise stated. CO gas was purchased from PanGas in 3.8 quality.

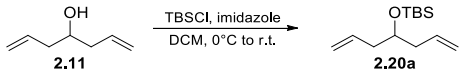
Instrumentation:

HPLC analyses were performed using a Shimadzu Prominence system with SIL-20A auto sample, CTO-20AC column oven, LC-20AD pump system, DGU-20A3 degasser and SPD M20A Diode Array or UV/VIS detector. The following chiral columns from Daicel Chemical Industries were used: OD-H (chiralcel), OJ-H (chiralcel) or IA (chiralpak) in 4.6 x 250 mm size. Infrared spectra were taken on a Bruker ALPHA FT-IR spectrometer and are reported in reciprocal centimeters (cm^{-1}). Nuclear magnetic resonance spectra were recorded on a Bruker Advance 250 (250 MHz), Bruker Advance 400 (400 MHz), Bruker Advance 500 (500 MHz) in deuterated chloroform (residual peaks ^{1}H δ = 7.26 ppm, ^{13}C δ = 77.16 ppm) unless otherwise noted. ^{31}P NMR spectra were on a Bruker Advance 400 (400 MHz). ^{19}F spectra were referenced to external $CFCl_3$. ^{31}P spectra were referenced to external 95% solution of H_3PO_4. Data are reported in parts per million (ppm) as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, sept = septuplet, m = multiplet and br s = broad signal), coupling constant in Hz and integration. High resolution mass spectra were

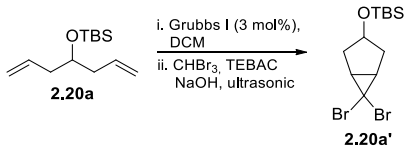
recorded by Dr. H. Nadig (Department of Chemistry, University of Basel) on a Bruker maXis 4G QTOF ESI mass spectrometer. Optical rotations were measured on a Perkin Elmer 341 Polarimeter in a 1 mL micro cuvette (cell length 100mm) with NaD-Line (λ = 589 nm) at 20 °C.

2. Chapter II : Divergent synthesis of aeruginosinsn based on a C(sp^3)–H activation strategy

2.1. Nucleophilic substitution study

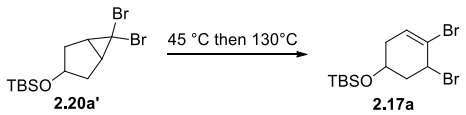


To a solution of 1,6-heptadien-4-ol (**2.11**) (2 g, 17.8 mmol) and imidazole (1.58 g, 23.2 mmol) in DCM (12 mL) under argon, tert-butylchlorodimethylsilane (3.5 g, 23.2 mmol) was added at 0 °C. The resulting mixture was stirred at room temperature during 16 hours. The reaction was quenched with an aqueous solution of $NaHCO_3$ saturated and then extracted three times with ethyl acetate. The combined organic layers were washed with water, brine, dried over $MgSO_4$, filtered and concentrated under vacuum at 40°C. The crude mixture mixture was purified by column chromatography (SiO_2, pentane / Et_2O, 1/0 to 99/1) to give the compound **2.20a** (3.8 g, 95%) as colorless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 5.92 – 5.71 (m, 2H), 5.09 – 5.04 (m, 2H), 5.02 (t, J = 2.5 Hz, 2H), 3.75 (p, J = 5.8 Hz, 1H), 2.31 – 2.13 (m, 4H), 0.92 – 0.88 (m, 9H), 0.08 – 0.04 (m, 6H).**^{13}C NMR (75MHz, $CDCl_3$)** δ = 135.4, 117.0, 71.9, 41.7, 26.0, 18.3, -4.3. **HRMS (ESI):** calculated for $C_{13}H_{27}OSi$ 227.1831 found 227.1836.



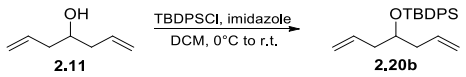
To a solution of **2.20a** (3.3 g, 14.6 mmol) in DCM (51 mL) under argon, Grubbs I (301 mg, 0.37 mmol) was added in one portion. The resulting mixture was stirred at room temperature during 20 min and then concentrated under vacuum at 40 °C until the half volume was evaporated. After, NaOH (3.51 g, 87.7 mmol) and benzyltriethylammonium chloride (167 mg, 0.73 mmol) was added to the resulting mixture followed by $CHBr_3$ (2.6 mL, 29.2 mmol). The resulting mixture was placed in ultrasonic bath during 6 hours. After, the brown solid was removed by filtration through a pad of sand and rinced with DCM. The filtrate was concentrated under vacuum at 40 °C. The crude mixture mixture was purified by column chromatography (SiO_2, pentane / Et_2O, 1/0 to 99/1) to give the compound **2.20a'** (5 g, 92%) as yellow oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 4.47 – 4.23 (m, 1H), 2.31 (d, J = 5.2 Hz, 2H), 2.13 (dd, J = 14.8, 6.8 Hz, 2H), 1.93 (ddd, J = 10.2, 8.1, 4.2 Hz, 2H), 0.86 (s, 9H), 0.01 (s, 6H).

^{13}C NMR (75MHz, $CDCl_3$) δ = 76.3, 42.0, 40.2, 37.9, 26.0, 18.2, -4.7. **HRMS (ESI):** calculated for $C_{12}H_{23}Br_2OSi$ 368.9885 found 368.9885.



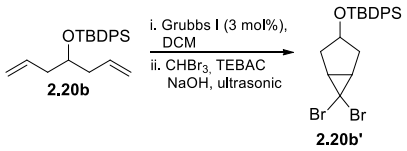
2.20a' **2.17a**

2.20a' (3.7 g, 10.1 mmol) was then heated neat at 45 °C during 6 hours and then at 130 °C during 1 hour. The crude mixture mixture was purified by column chromatography (SiO_2, pentane / DCM, 1/0 to 97/3) to give the compound **2.17a** (3.2 g, 87%) as a mixture of diastereoisomers in 6 to 1 ratio and as a yellow oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 6.06 (dd, *J* = 5.6, 2.7 Hz, 1H), 4.79 (s, 1H), 4.47 – 4.27 (m, 1H), 2.57 – 2.44 (m, 1H), 2.42 – 2.33 (m, 1H), 2.27 – 2.12 (m, 2H), 0.89 (s, 9H), 0.10 (s, 6H).**^{13}C NMR (75MHz, $CDCl_3$)** δ = 132.2, 121.9, 63.3, 53.4, 42.6, 37.5, 25.9, 18.2, -4.6, -4.6. **HRMS (ESI):** calculated for $C_{12}H_{23}Br_2OSi$ 368.9885 found 368.9885.

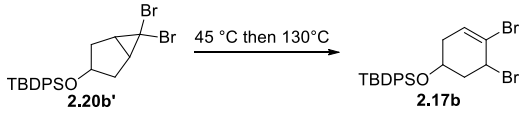


2.11 **2.20b**

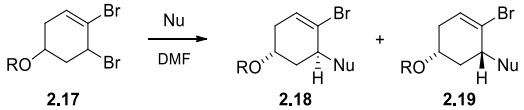
To a solution of 1,6-heptadien-4-ol (**2.11**) (2 g, 17.8 mmol) and imidazole (1.58 g, 23.2 mmol) in DCM (12 mL) under argon, tert-butylchlorodiphenylsilane (6.37 g, 23.2 mmol) was added at 0 °C. The resulting mixture was stirred at room temperature during 16 hours. The reaction was quenched with an aqueous solution of $NaHCO_3$ saturated and then extracted three times with ethyl acetate. The combined organic layers were washed with water, brine, dried over $MgSO_4$, filtered and concentrated under vacuum at 40°C. The crude mixture mixture was purified by column chromatography (SiO_2, pentane / Et_2O, 1/0 to 99/1) to give the compound **2.20b** (6.3 g, 100%) as colorless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 7.77 – 7.69 (m, 4H), 7.49 – 7.38 (m, 6H), 5.79 (ddt, J = 17.3, 10.3, 7.1 Hz, 2H), 5.07 – 4.92 (m, 4H), 3.93 – 3.82 (m, 1H), 2.38 – 2.14 (m, 4H), 1.12 (s, 9H).**^{13}C NMR (75MHz, $CDCl_3$)** δ =136.1, 134.9, 134.5, 129.7, 127.6, 117.2, 72.6, 40.7, 27.2, 19.5. **HRMS (ESI):** calculated for $C_{23}H_{31}OSi$ 351.2144 found 351.2148.



To a solution of **2.20b** (6.3 g, 17.9 mmol) in DCM (63 mL) under argon, Grubbs I (367 mg, 0.45 mmol) was added in one portion. The resulting mixture was stirred at room temperature during 20 min and then concentrated under vacuum at 40 °C until the half volume was evaporated. After, NaOH (4.3 g, 107 mmol) and benzyltriethylammonium chloride (203 mg, 0.89 mmol) was added to the resulting mixture followed by $CHBr_3$ (3.1 mL, 35.7 mmol). The resulting mixture was placed in ultrasonic bath during 6 hours. After, the brown solid was removed by filtration through a pad of sand and rinced with DCM. The filtrate was concentrated under vacuum at 40 °C. The crude mixture was purified by column chromatography (SiO_2, pentane / Et_2O, 1/0 to 99/1) to give the compound **2.20b'** (8.7 g, 99%) as yellow oil. **^{1}H NMR (300 MHz, $CDCl_3$)** complex mixture of isomers. **^{13}C NMR (75MHz, $CDCl_3$)** complex mixture of isomers. **HRMS (ESI):** calculated for $C_{22}H_{27}Br_2OSi$ 493.0198 found 493.0194.

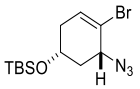


2.20b' (5.9 g, 11.92 mmol) was then heated neat at 45 °C during 6 hours and then at 130 °C during 1 hour. The crude mixture mixture was purified by column chromatography (SiO_2, pentane / DCM, 1/0 to 97/3) to give the compound **2.17b** (5.1 g, 88%) as a mixture of diastereoisomers in 6 to 1 ratio and as a yellow oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 7.71 – 7.62 (m, 4H), 7.47 – 7.35 (m, 6H), 6.06 – 5.91 (m, 1H), 4.73 – 4.58 (m, 1H), 4.49 – 4.31 (m, 1H), 2.54 – 2.08 (m, 4H), 1.06 (s, 9H).). **^{13}C NMR (75MHz, $CDCl_3$, mixture of isomers)** δ = 135.8, 135.7, 135.6, 133.9, 133.7, 131.9, 131.2, 129.9, 129.9, 129.5, 127.8, 127.8, 127.6, 121.8, 66.2, 64.1, 52.7, 49.8, 43.4, 42.1, 37.1, 36.5, 27.0, 26.9, 19.2. **HRMS (ESI):** calculated for $C_{22}H_{27}Br_2OSi$ 493.0198 found 493.0195.



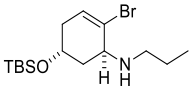
General procedure: To a solution of **2.17** in DMF (1 M), the nucleophile (6 equiv.) and K_2CO_3 (1.1 equiv.) when the amine was used as nucleophile, were added and the resulting mixture stirred during 16 hours at room temperature.

The reaction was then quenched with water and extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum at 40 °C. The diastereoselectivity was observed by ^1H NMR analysis in the crude mixture mixture. Then, the crude mixture was purified in silica gel to confirm the formation of the compound.



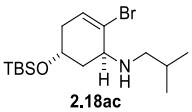
2.19aa

Following the general procedure, **2.17a** (250 mg, 0.68 mmol) and sodium azide were used leading to a 1:8 ratio of diastereoisomers. The purification of the crude mixture (pentane / AcOEt 1/0 to 97/3) afforded 183 mg (82%) of **2.19aa** with a diastereoisomeric ratio of 1:6. **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 6.24 – 6.09 (m, 1H), 4.03 – 3.95 (m, 1H), 2.36 – 2.22 (m, 2H), 2.21 – 2.12 (m, 1H), 2.12 – 1.97 (m, 1H), 1.97 – 1.83 (m, 1H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H).**^{13}C NMR (75MHz, $CDCl_3$)** δ = 131.4, 120.7, 64.8, 61.6, 39.0, 36.9, 25.9, 18.3, -4.6, -4.8.



2.18ab

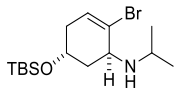
Following the general procedure, **2.17a** (100 mg, 0.27 mmol) and propylamine were used leading to a 3:1 ratio of diastereoisomers. The purification of the crude mixture (pentane / AcOEt 1/0 to 9/1) afforded 22 mg (23%) of **2.18ab** with a diastereoisomeric ratio of 1:0. **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 6.04 – 5.96 (m, 1H), 4.19 – 4.05 (m, 1H), 3.49 – 3.35 (m, 1H), 2.68 – 2.46 (m, 2H), 2.31 (dt, J = 17.3, 5.0 Hz, 1H), 2.09 – 1.90 (m, 2H), 1.87 – 1.74 (m, 1H), 1.62 – 1.45 (m, 3H), 0.95 (t, J = 7.4 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.06 (s, 3H).**^{13}C NMR (75MHz, $CDCl_3$)** δ = 129.3, 125.7, 64.0, 59.2, 49.1, 37.8, 37.4, 26.0, 23.6, 18.3, 12.0, -4.6.



2.18ac

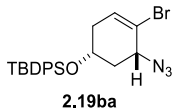
Following the general procedure, **2.17a** (100 mg, 0.27 mmol) and isobutylamine were used leading to a 3:1 ratio of diastereoisomers. The purification of the crude mixture (pentane / AcOEt 1/0 to 9/1) afforded 58 mg (59%) of **2.18ac** with a diastereoisomeric ratio of 1:0.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.04 – 5.93 (m, 1H), 4.14 – 4.05 (m, 1H), 3.38 (s, 1H), 2.41 (d, J = 6.6 Hz, 2H), 2.36 – 2.27 (m, 1H), 2.08 – 1.93 (m, 2H), 1.80 – 1.69 (m, 2H), 1.52 (s, 1H), 0.96 – 0.91 (m, 6H), 0.88 (s, 9H), 0.06 (s, 3H), 0.06 (s, 3H).**^{13}C NMR (75MHz, $CDCl_3$)** δ = 129.4, 125.7, 64.0, 59.7, 55.6, 38.0, 37.5, 28.9, 26.1, 21.0, 20.9, 18.3, -4.5.



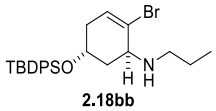
2.18ad

Following the general procedure, **2.17a** (150 mg, 0.42 mmol) and isopropylamine were used leading to a 6:1 ratio of diastereoisomers. The purification of the crude mixture (pentane / AcOEt 1/0 to 9/1) afforded 58 mg (59%) of **2.18ad** with a diastereoisomeric ratio of 1:0**. ^{1}H NMR (300 MHz, $CDCl_3$)** δ = 5.94 (dd, J = 5.2, 2.9 Hz, 1H), 4.15 – 4.04 (m, 1H), 3.41 (s, 1H), 2.98 – 2.81 (m, 1H), 2.31 (dt, J = 17.3, 5.2 Hz, 1H), 2.07 – 1.87 (m, 2H), 1.82 – 1.66 (m, 2H), 1.10 – 1.04 (m, 6H), 0.89 (s, 10H), 0.07 (s, 3H), 0.06 (s, 3H). **^{13}C NMR (75MHz, $CDCl_3$)** δ = 129.2, 125.4, 63.7, 57.8, 47.4, 39.5, 37.5, 26.0, 24.5, 22.6, 18.3, -4.6.



2.19ba

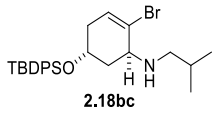
Following the general procedure, **2.17b** (250 mg, 0.51 mmol) and sodium azide were used leading to a 1:15 ratio of diastereoisomers. The purification of the crude mixture (pentane / AcOEt 1/0 to 97/3) afforded 199 mg (86%) of **2.19ba** with a diastereoisomeric ratio of 1:15. **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 7.74 – 7.66 (m, 4H), 7.48 – 7.40 (m, 6H), 6.16 – 5.97 (m, 1H), 4.02 – 3.92 (m, 1H), 3.93 – 3.84 (m, 1H), 2.33 – 2.23 (m, 1H), 2.26 – 2.17 (m, 2H), 2.08 – 1.93 (m, 1H), 1.12 (s, 9H). **^{13}C NMR (75MHz, $CDCl_3$)** δ = 135.8, 133.8, 133.7, 131.2, 130.0, 130.0, 127.9, 127.8, 121.0, 65.9, 61.8, 38.9, 36.6, 27.0, 19.2.



2.18bb

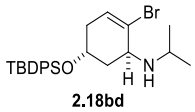
Following the general procedure, **2.17b** (250 mg, 0.51 mmol) and propylamine were used leading to a 7:1 ratio of diastereoisomers. The purification of the crude mixture (pentane / AcOEt 1/0 to 9/1) afforded 98 mg (41%) of **2.18bb** with a diastereoisomeric ratio of 14:1.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.76 – 7.62 (m, 4H), 7.50 – 7.33 (m, 6H), 5.96 (t, J = 3.9 Hz, 1H), 4.25 – 3.86 (m, 1H), 3.41 (t, J = 4.5 Hz, 1H), 2.53 – 2.18 (m, 3H), 2.17 – 2.05 (m, 1H), 1.96 – 1.79 (m, 2H), 1.46 – 1.30 (m, 3H), 1.08 (s, 9H), 0.88 (t, J = 7.4 Hz, 3H).**^{13}C NMR (75MHz, $CDCl_3$)** δ = 135.9, 135.8, 134.3, 134.2, 129.8, 129.8, 129.0, 127.7, 127.7, 125.9, 65.0, 58.9, 48.5, 37.3, 37.0, 27.0, 23.4, 19.3, 11.9.



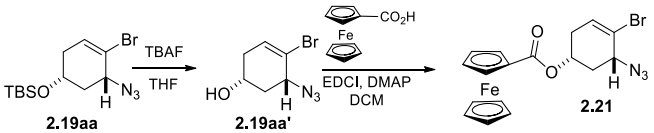
2.18bc

Following the general procedure, **2.17b** (250 mg, 0.51 mmol) and isobutylamine were used leading to a 8:1 ratio of diastereoisomers. The purification of the crude mixture (pentane / AcOEt 1/0 to 9/1) afforded 122 mg (50%) of **2.18bc** with a diastereoisomeric ratio of 14:1. **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 7.76 – 7.66 (m, 4H), 7.49 – 7.37 (m, 6H), 5.97 (t, J = 3.9 Hz, 1H), 4.30 – 3.92 (m, 1H), 3.42 (t, J = 4.3 Hz, 1H), 2.36 – 2.06 (m, 4H), 2.01 – 1.81 (m, 2H), 1.69 – 1.52 (m, 1H), 1.45 (br. s, 1H), 1.10 (s, 9H), 0.89 (d, J = 6.5 Hz, 6H). **^{13}C NMR (75MHz, $CDCl_3$)** δ = 135.8, 135.8, 134.3, 134.2, 129.8, 129.8, 128.9, 127.7, 127.7, 125.9, 65.0, 59.0, 54.7, 37.5, 37.0, 28.6, 27.1, 20.8, 20.7, 19.3.



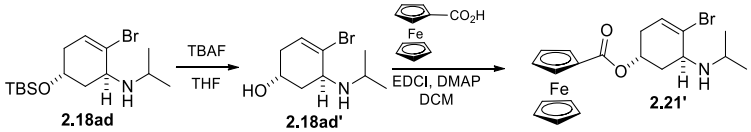
2.18bd

Following the general procedure, **2.17b** (310 mg, 0.65 mmol) and isopropylamine were used leading to a 11:1 ratio of diastereoisomers. The purification of the crude mixture (pentane / AcOEt 1/0 to 9/1) afforded 217 mg (73%) of **2.18bd** with a diastereoisomeric ratio of 11:1. **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.60 – 7.53 (m, 4H), 7.31 – 7.21 (m, 6H), 5.75 (s, 1H), 4.17 – 3.87 (m, 1H), 3.28 (s, 1H), 2.85 – 2.46 (m, 1H), 2.24 – 2.06 (m, 1H), 2.07 – 1.89 (m, 2H), 1.87 – 1.64 (m, 2H), 1.00 – 0.95 (m, 9H), 0.86 (d, J = 6.0 Hz, 3H), 0.80 (d, J = 6.2 Hz, 4H).**^{13}C NMR (75MHz, $CDCl_3$)** δ =135.9, 135.8, 134.4, 134.3, 129.8, 129.8, 128.7, 127.8, 127.7, 125.6, 64.6, 57.1, 46.7, 38.9, 37.2, 27.1, 24.3, 22.4, 19.3.



To a solution of **2.19aa** (170 mg, 0.37 mmol) in THF (0.5 mL), a solution of TBAF in THF (450 µL, 0.450 mmol, 1M) was added dropwise at 0 °C. The resulting mixture was stirred at room temperature during 16h and quenched with water. The mixture was then extracted with

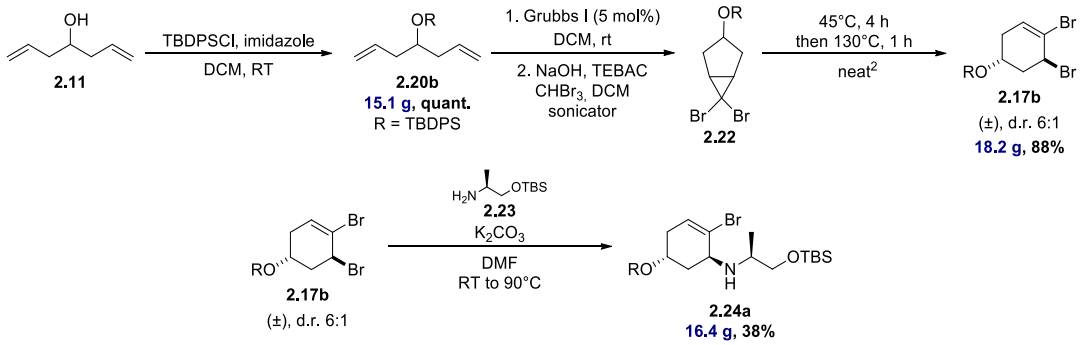
ethyl acetate three times. The combined organic layers was washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum at 40 °C. . The crude mixture was filtrated on a short pad of which gave the compound **2.19aa'** pure enough to be engaged in esterification. To a mixture of ferrocencarboxylic acid (44.8 mg, 0.2 mmol), EDCI (44.8 mg, 0.23 mmol) and DMAP (4.8 mg, 0.04 mmol), a solution of **2.19aa'** (51 mg, 0.23 mmol) in DCM (0.7 mL) was added at 0 °C. The resulting mixture was stirred at room temperature during 16 h and quenched with brine. The reaction was then extracted with DCM three times and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum at 40 °C. The crude mixture was purified by preparative TLC (SiO_2, pentane / AcOEt 1/0 to 9/1) which gave the compound **2.21** (48 mg, 35 % over two steps) as brown crystal. **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 6.28 (t, J = 3.8 Hz, 1H), 5.34 – 5.18 (m, 1H), 4.91 – 4.78 (m, 2H), 4.41 (t, J = 1.9 Hz, 2H), 4.25 – 4.15 (m, 6H), 2.53 (dt, J = 17.7, 4.5 Hz, 1H), 2.45 – 2.39 (m, 1H), 2.39 – 2.33 (m, 1H), 2.21 (ddd, J = 13.8, 7.7, 6.2 Hz, 1H). **^{13}C NMR (75MHz, $CDCl_3$)** δ = 171.4, 130.5, 120.5, 71.7, 70.8, 70.6, 70.3, 69.9, 64.9, 60.7, 34.7, 33.0. **HRMS (ESI):** calculated for $C_{17}H_{17}BrFeN_3O_2$ 429.9854 found 429.9850.



To a solution of **2.18ad** (279 mg, 0.59 mmol) in THF (0.7 mL), a solution of TBAF in THF (709 µL, 0.71 mmol, 1M) was added dropwise at 0 °C. The resulting mixture was stirred at room temperature during 16h and quenched with water. The mixture was then extracted with ethyl acetate three times. The combined organic layers was washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum at 40 °C. The crude mixture was filtrated on a short pad of which gave the compound **2.18ad'** pure enough to be engaged in esterification. To a mixture of ferrocencarboxylic acid (45.9 mg, 0.2 mmol), EDCI (45.8 mg, 0.24 mmol) and DMAP (4.9 mg, 0.04 mmol), a solution of **2.18ad'** (56 mg, 0.24 mmol) in DCM (0.7 mL) was added at 0 °C. The resulting mixture was stirred at room temperature during 16 h and quenched with brine. The reaction was then extracted with DCM three times and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under vacuum at 40 °C. The crude mixture was purified by preparative TLC (SiO_2, pentane / AcOEt 1/0 to 9/1) which gave the compound **2.21'** (26 mg, 11 % over two steps) as brown crystal.

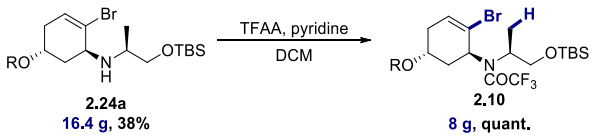
^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.04 (t, J = 3.8 Hz, 1H), 5.46 – 5.10 (m, 1H), 4.92 – 4.65 (m, 2H), 4.50 – 4.30 (m, 2H), 4.19 (s, 5H), 3.66 – 3.37 (m, 1H), 2.98 (sept, J = 6.2 Hz, 1H), 2.59 (dt, J = 9.5, 4.5 Hz, 1H), 2.31 – 2.16 (m, 1H), 2.16 – 1.95 (m, 2H), 1.41 (br s, 1H), 1.12 (d, J = 6.2 Hz, 3H), 1.09 (d, J = 6.2 Hz, 3H). **^{13}C NMR (75MHz, $CDCl_3$)** δ = (C=O) is missing, 127.9, 125.9, 71.5, 70.3, 69.9, 66.1, 56.8, 47.4, 35.9, 33.5, 24.3, 22.8. **HRMS (ESI):** calculated for $C_{20}H_{25}BrFeNO_2$ 446.0418 found 446.0420.

2.2. Synthesis of the Choi Core



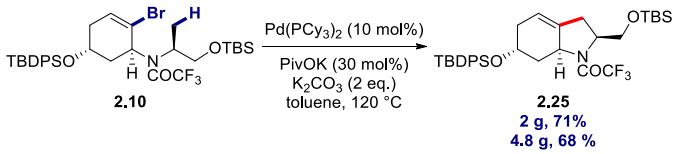
To a solution of 1,6-heptadien-4-ol (**2.11**) (5 g, 43.2 mmol) and imidazole (3.83 g, 56.3 mmol) in DCM (30 mL) under argon, tert-butylchlorodiphenylsilane (14.6 mL, 56.2 mmol) was added at 0 °C. The resulting mixture was stirred at room temperature during 16 hours. The reaction was quenched with an aqueous solution of $NaHCO_3$ saturated and then extracted three times with ethyl acetate. The combined organic layers were washed with water, brine, dried over $MgSO_4$, filtered and concentrated under vacuum at 40°C. The resulting residue was absorbed on a pad of silica gel (diameter 7 cm, length 10 cm) and filtered off using a mixture of pentane / Et_2O (9/1, 300 mL). The filtrate was concentrated under vacuum at 40 °C. To a solution of the crude mixture product in DCM (140 mL) under argon, Grubbs I (1.08 g, 1.3 mmol) was added in one portion. The resulting mixture was stirred at room temperature during 20 min and then concentrated under vacuum at 40 °C until the half volume was evaporated. After, NaOH (10.5 g, 262.6 mmol) and benzyltriethylammonium chloride (500 mg, 2.19 mmol) was added to the resulting mixture followed by $CHBr_3$ (7.7 mL, 87.5 mmol). The resulting mixture was placed in ultrasonic bath during 6 hours. After, the brown solid was removed by filtration through a pad of sand and rinced with DCM. The filtrate was concentrated under vacuum at 40 °C and absorbed on a pad of silica gel (diameter 7 cm, length 10 cm) and filtered off using a mixture of pentane / Et_2O (9/1, 2 L). The filtrate was concentrated under vacuum at 40 °C. The crude mixture product was then heated neat at 45 °C during 6 hours and then at 130 °C during 1 hour.

The resulting mixture was then dissolved in DMF (100 mL) and K_2CO_3 (6.4 g, 46.6 mmol) was added followed by (*S*)-1-((tert-butyldimethylsilyl)oxy)propan-2-amine[181] (**2.23**) (32.1 g, 169.5 mmol). The resulting mixture was stirred at room temperature during 16 hours and then 90 °C during 6 hours. After, the mixture was quenched with an aqueous solution of $NaHCO_3$ saturated and then extracted three times with ethyl acetate. The combined organic layers were washed with water, brine, dried over $MgSO_4$, filtered and concentrated at 40 °C under vacuum. Finally, the crude mixture mixture of diastereoisomer was purified by column chromatography (SiO_2, pentane / Et_2O 1/0 to 95/5) which gave the compound **2.24a** (8 g, 33 %) as slightly yellow oil. **$[\alpha]_D$=** – 18.9 ° ($CHCl_3$, c 0.95). **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 0.1 (s, 6 H) 0.9 (s, 9 H) 1.0 (d, *J*=6.4 Hz, 3 H) 1.1 (s, 9 H) 1.34 (br. s, 1H) 1.8 - 1.9 (m, 2 H) 2.1 (dddd, *J*=17.3, 7.5, 3.4, 1.5 Hz, 1 H) 2.3 (dt, *J*=17.3, 4.9 Hz, 1 H) 2.5 - 2.6 (m, 1 H) 3.3 (dd, *J*=9.5, 5.7 Hz, 1 H) 3.4 (dd, *J*=9.5, 4.6 Hz, 1 H) 3.5 (t, *J*=4.4 Hz, 1 H) 4.1 - 4.3 (m, 1 H) 5.9 (dd, *J*=4.6, 3.5 Hz, 1 H) 7.3 - 7.5 (m, 6 H) 7.6 - 7.8 (m, 4 H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ = -5.4, -5.4, 16.7, 18.2, 19.1, 25.9, 26.9, 37.0, 38.5, 52.0, 56.3, 64.6, 68.0, 125.5, 127.5, 127.6, 128.4, 129.6, 129.6, 134.2, 134.3, 135.7, 135.7. **HRMS (ESI):** calculated for $C_{31}H_{49}BrNO_2Si_2$ 602.2480 found 602.2498.

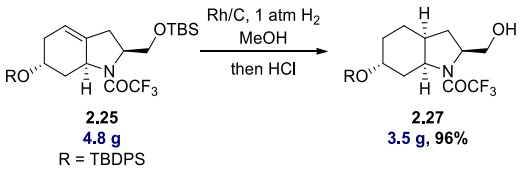


2.24a 16.4 g, 38% **2.10** 8 g, quant.

To a solution of **2.24a** (7.5 g, 12.42 mmol) and pyridine (3 mL, 37.25 mmol) in DCM (180 mL), trifluoroacetic anhydride (5.2 mL, 37.25 mmol) was added dropwise at 0°C. The mixture was then stirred 16 hours at room temperature and quenched with a saturated aqueous solution of $NaHCO_3$. The resulting mixture was extracted with ethyl acetate three times and the combined organic layers were washed with water, brine, filtered, dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture mixture was purified by column chromatography (SiO_2, pentane / Et_2O, 1/0 to 95/5) to give the compound **2.10** (8.7 g, 100%) as colorless oil. **$[\alpha]_D$=** – 40.7 ° ($CHCl_3$, c 1.33). **^{1}H NMR (300 MHz, $CDCl_3$)** complex mixture of rotamers. **^{13}C NMR (75 MHz, $CDCl_3$)** complex mixture of rotamers. **^{19}F NMR (282 MHz, $CDCl_3$, major rotamer)** δ =– 69.2 **HRMS (ESI):** calculated for $C_{33}H_{48}BrF_3NO_3Si_2$ 698.2303 found 698.2310.

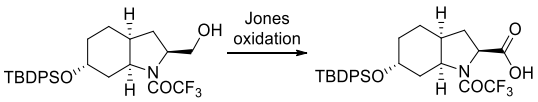


A flame dried schlenk tube was introduced in a glovebox and was charged with $Pd(PCy_3)_2$ (754 mg, 1.13 mmol), potassium pivalate (475 mg, 3.39 mmol) and K_2CO_3 (3.12 g, 22.6 mmol). The schlenk was then removed from the glovebox and a solution of **2.10** (7.89 g, 11.3 mmol) in distilled toluene (57 mL) was added in the schlenk tube under argon. The resulting mixture was then heated at 120 °C during 24 hours. The brownish mixture was then filtered through a pad of celite and concentrated *in vacuo*. Purification by column chromatography (SiO_2, pentane/ Et_2O, 1/0 to 98/2) gave the compound **2.25** (4.77 g, 68 %) as slightly yellow solid. **m.p.** = 113.2 °C. **$[\alpha]_D$**= + 21.5 ° ($CHCl_3$, c 1.13). **^{1}H NMR (300 MHz, $CDCl_3$, major rotamer)** δ = 0.03 (s, 6 H) 0.86 - 0.92 (m, 9 H) 0.90 - 0.99 (m, 1 H) 1.10 (s, 9 H) 2.12 - 2.24 (m, 2 H) 2.58 - 2.74 (m, 2 H) 2.84 (dt, *J*=12.0, 4.5 Hz, 1 H) 3.20 (t, *J*=9.8 Hz, 1 H) 3.58 (dd, *J*=9.6, 4.1 Hz, 1 H) 4.15 - 4.34 (m, 2 H) 4.74 - 4.91 (m, 1 H) 5.56 - 5.66 (m, 1 H) 7.31 - 7.54 (m, 6 H) 7.56 - 7.82 (m, 4 H). **^{13}C NMR (75 MHz, $CDCl_3$, major rotamer)** δ = 136.0, 135.8, 134.5, 134.3, 133.5, 129.8, 129.6, 127.7, 127.6, 120.0, 116.3 (q, $J_{C\text{-}F}$ =288 Hz), 66.1, 63.2, 60.6, 59.4 (q, $J_{C\text{-}F}$ =2.7 Hz), 55.1, 34.9, 34.1, 34.0, 27.0, 25.8, 19.3, 18.3, -5.4, -5.5 CO is missing. **^{19}F NMR (282 MHz, $CDCl_3$, major rotamer)** δ =- 70.57. **HRMS (ESI):** calculated for $C_{33}H_{47}F_3NO_3Si_2$ 618.3041 found 618.3030.



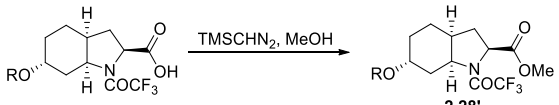
To a solution of **2.25** (4.4 g, 7.28 mmol) in EtOAc (36 mL), Rh/C (5 % wt) (3 g, 1.48 mmol) was added and the atmosphere was replaced by H_2 *via* vacuum / H_2 cycle (three times). The resulting mixture was stirred 16 hours at room temperature and then was filtered through a pad of celite. The filtrate was concentrated *in vacuo* and the residue was dissolved in $CHCl_3$ (40 mL). At 0°C, a solution 0.5% HCl methanolic (prepared from 226 mL of MeOH and 1.7 mL of Acetyl chloride) was added and stirred during 1 hour at room temperature. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$. The resulting mixture was extracted three times with ethyl acetate and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, pentane/ AcOEt, 1/0 to 98/2) gave the compound **2.27** (3.5 g, 95%) as a colorless oil.

[α]$_D$= + 1.17 ° ($CHCl_3$, c 1). **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 1.1 (s, 9 H) 1.3 - 1.7 (m, 4 H) 1.7 - 2.1 (m, 3 H) 2.2 - 2.5 (m, 2 H) 3.6 (dd, *J*=10.9, 5.5 Hz, 1 H) 3.7 - 3.9 (m, 2 H) 4.1 - 4.2 (m, 1 H) 4.2 - 4.3 (m, 1 H) 4.6 (dt, *J*=11.3, 5.5 Hz, 1 H) 7.3 - 7.5 (m, 6 H) 7.6 - 7.8 (m, 4 H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ = 157.2 (q, J_{C-F} =37 Hz), 135.8, 135.7, 134.1, 133.7, 129.8, 129.8, 127.7, 127.7, 116.6 (q, J_{C-F} =288 Hz), 67.5, 64.5, 62.7, 56.3 (q, J_{C-F} =2.3 Hz), 36.6, 34.3, 28.1, 27.0, 26.2, 19.4, 19.2. **^{19}F NMR (282 MHz, $CDCl_3$)** δ =– 70.6. **HRMS (ESI):** calculated for $C_{27}H_{35}F_3NO_3Si$ 506.2333 found 506.2326.



2.27 **3.5 g** **2.28** **3.1 g, 86%**

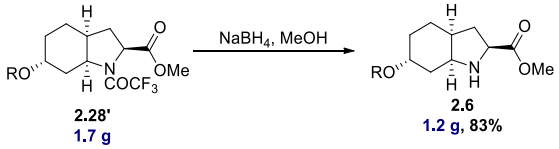
To a solution of **2.27** (3.5 g, 6.92 mmol) in acetone (53 mL) at 0°C, Jones reagent (8 mL, 21.56 mmol, 2.7 M) was added dropwise. After 3 hours at 0 °C, isopropanol (13 mL) was added and the resulting mixture was stirred 1 hour at room temperature. The reaction was then extracted with ethyl acetate three times and the combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and dried *in vacuo*. Purification by column chromatography (SiO_2, pentane/ AcOEt / AcOH (1 %), 9/1 to 6/4) gave the compound **2.28** (3.1 g, 86 %) as a colorless oil. **[α]$_D$=** – 23.2 ° ($CHCl_3$, c 1.55). **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 1.1 (s, 9 H) 1.3 - 1.5 (m, 2 H), 1.5 - 1.7 (m, 2 H), 2.0 - 2.2 (m, 2 H), 2.2 - 2.5 (m, 2 H), 2.5 - 2.7 (m, 1 H), 4.1 (br. s., 1 H), 4.6 (t, *J*=9.2 Hz, 1 H), 4.7 (dt, *J*=11.1, 5.5 Hz, 1 H), 7.3 - 7.5 (m, 6 H), 7.6 - 7.8 (m, 4 H), 11.3 (br. s., 1 H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ = 19.3, 19.3, 26.1, 27.0, 29.2, 33.9, 37.6, 56.4 (br), 60.0, 67.4, 116.2 (q, J_{C-F}=286.5 Hz), 127.7, 127.8, 129.8, 129.9, 133.6, 134.0, 135.7, 135.7, 155.9 (q, J_{C-F}= 38.4 Hz) 176.8. **^{19}F NMR (282 MHz, $CDCl_3$)** δ =– 71.0. **HRMS (ESI):** calculated for $C_{27}H_{33}F_3NO_4Si$ 520.2125 found 520.2124.



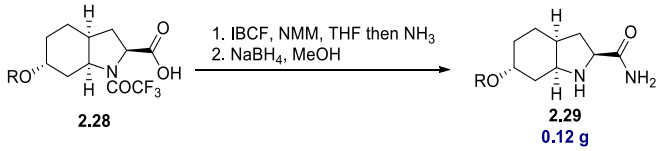
2.28 **3.1 g** **2.28'** **1.7 g, 97%**

To a solution of **2.28** (1.7 g, 3.27 mmol) in MeOH (16 mL) at 0 °C, a solution of $TMSCHN_2$ in hexane (2M, 8.2 mL, 16.96 mmol) was added dropwise. After 30 min at 0 °C, acetic acid (1.7 mL) was added and the resulting mixture was concentrated *in vacuo*. Purification by column chromatography (SiO_2, pentane/ AcOEt, 9/1 to 6/4) gave the compound **2.28'**(1.7 g, 97 %) as a colorless oil. **[α]$_D$=** – 17.6 ($CHCl_3$, c 1.72).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.15 (s, 9 H), 1.30 - 1.48 (m, 2 H), 1.48 - 1.69 (m, 2 H), 1.90 - 2.15 (m, 2 H), 2.21 - 2.46 (m, 2 H), 2.46 - 2.62 (m, 1 H), 3.75 (s, 3 H), 4.15 (br. s., 1 H), 4.58 (t, *J*=9.3 Hz, 1 H), 4.67 (dt, *J*=11.6, 5.9 Hz, 1 H), 7.36 - 7.51 (m, 6 H), 7.67 – 7.75 (m, 4 H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ = 171.5, 155.6 (q, J_{C-F} = 37.3 Hz), 135.57, 135.53, 133.85, 133.39, 129.71, 129.62, 127.56, 127.50, 116.1(q, J_{C-F} = 286.5 Hz),, 67.3, 59.9, 56.0 (q, J_{C-F} = 2.2 Hz), 52.3, 37.4, 33.8, 29.2, 26.8, 26.0, 19.2, 19.1. **^{19}F NMR (282 MHz, $CDCl_3$)** δ = – 71.0. **HRMS (ESI):** calculated for $C_{28}H_{35}F_3NO_4Si$ 534.2282 found 534.2271.



To a solution of **2.28'** (1.68 g, 3.15mmol) in MeOH (31 mL) at 0°C, $NaBH_4$ (715 mg, 18.89 mmol) was added in one portion. After 2 hours at 0 °C, a spatula of silica gel was added and the resulting mixture was concentrated *in vacuo*. Purification by column chromatography (SiO_2, pentane/ AcOEt / Et_3N (1 %), 9/1 to 1/1) gave the compound **2.6** (1.15 g, 83 %) as a colorless oil. **$[\alpha]_D$=** – 10.35 ° ($CHCl_3$, c 1.25). **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 1.08 (s, 9 H) 1.16 - 1.46 (m, 3 H) 1.52 - 1.80 (m, 4 H) 2.00 - 2.22 (m, 2 H) 2.52 (br. s., 1 H) 3.36 (q, *J*=5.6 Hz, 1 H) 3.69 (s, 3 H) 3.77 (dd, *J*=9.5, 6.3 Hz, 1 H) 3.92 - 4.03 (m, 1 H) 7.33 - 7.47 (m, 6 H) 7.64 - 7.72 (m, 4 H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ = 176.0, 135.6, 134.5, 134.3, 129.5, 129.4, 127.5, 127.4, 67.9, 58.4, 57.6, 52.0, 37.4, 36.3, 34.8, 31.7, 26.9, 24.0, 19.1. **HRMS (ESI):** calculated for $C_{26}H_{36}NO_3Si$ 438.2459 found 438.2450.



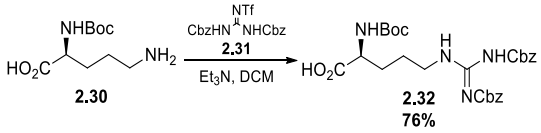
To a solution of **2.28** (198 mg, 0.381 mmol, 1 equiv) in THF (4 mL9 at 0°C under inert atmosphere, N-methylmorpholine (76 µL, 0.457 mmol, 1.2 equiv) was added followed by isobutyl chloroformate (60 µL, 0.457 mmol, 1.2 equiv) and the resulting mixture was stirred at 0°C during one hour. The, ammonia was bubbled into the resulting mixture during 15 minutes and the resulting mixture was stirred at room temperature overnight. The crude mixture was concentrated under reduce pressure and extracted with ethyl acetate, driedd over $MgSO_4$, filtered and concentrated under reduce pressure to afford the desired compound **2.28''** without further purification (163 mg, 0.314 mmol, 83%).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.77 – 7.57 (m, 4H), 7.47 – 7.35 (m, 6H), 6.72 (br s, 1H), 6.07 (br s, 1H), 4.73 – 4.44 (m, 2H), 4.18 – 4.06 (m, 1H), 2.53 – 2.38 (m, 1H), 2.36 – 2.21 (m, 2H), 2.15 – 2.04 (m, 1H), 1.98 – 1.81 (m, 1H), 1.69 – 1.56 (m, 2H), 1.54 – 1.37 (m, 2H), 1.11 (s, 9H). **^{19}F NMR (282 MHz, $CDCl_3$)** δ = –70.73. **^{13}C NMR (75 MHz, $CDCl_3$)** δ = 172.6, 156.5 (q, *J* = 37.4 Hz), 135.8, 135.7, 134.1, 133.7, 129.9, 129.8, 127.7, 127.7, 116.4 (q, *J* = 287.0 Hz), 67.5, 60.9, 56.8, 37.3, 33.7, 28.6, 27.0, 26.1, 19.4, 19.3.

To a solution of **2.28'**' (163 mg, 0.314 mmol) in MeOH (3.1 mL) at 0°C, $NaBH_4$ (35.7 mg, 0.943 mmol, 3 equiv) was added in one portion. After 2 hours at 0 °C, a spatula of silica gel was added and the resulting mixture was concentrated *in vacuo*. Purification by column chromatography (SiO_2, pentane/ AcOEt / Et_3N (1 %), 9/1 to 1/1) gave the compound **2.29** (118.2 mg, 0.28 mmo, 89 %) as a colorless oil.

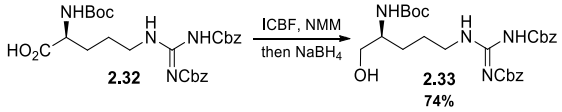
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.73 – 7.65 (m, 4H), 7.47 – 7.31 (m, 6H), 7.10 (br s, 1H), 5.79 (br s, 1H), 3.97 – 3.84 (m, 1H), 3.61 (dd, J = 10.9, 4.6 Hz, 1H), 3.46 (q, J = 4.8 Hz, 1H), 2.24 (ddd, J = 13.1, 10.9, 7.0 Hz, 1H), 2.04 (s, 1H), 1.97 – 1.85 (m, 1H), 1.77 – 1.52 (m, 4H), 1.43 – 1.16 (m, 3H), 1.07 (s, 9H).

2.3. Synthesis of the C-termini



To a solution of *N*-Boc L-orthinine **2.30** (1.14 g, 4.91 mmol) and Et_3N (0.82 mL, 5.89 mmol) in DCM (10 mL), *N*-methyl-*N*-trimethylsilyltrifluoroacetamide (2.15 g, 10.8 mmol) was added and heated until a clear solution was obtained. After cooling at room temperature, *N*,*N*'-di-Cbz-*N*''-trifluoromethanesulfonyl-guanidine[88] **2.31** (2.7 g, 5.89 mmol) was added in one portion and the reaction was stirred at room temperature during 16 hours. The reaction was then quenched with an aqueous solution of $NaHSO_4$ (2M) and extracted with DCM three times. The combined organic layers were washed with an aqueous solution of $NaHSO_4$ (2M) and water, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, pentane / AcOEt / 1% AcOH, 8/2 to 1/1) gave the compound **2.32** (2.02 g, 76 %) as a colourless oil. **$[\alpha]_D$**= + 14 ° ($CHCl_3$, c 1). **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 11.25 (br. s., 2 H) 8.29 (br. s., 1 H) 7.11 - 7.35 (m, 10 H) 5.24 (br. d., *J*=7.9 Hz, 1 H) 5.07 (s, 2 H) 5.03 (s, 2 H) 4.24 (br. s., 1 H) 3.34 (br. s., 2 H) 1.70 - 1.87 (m, 1 H) 1.46 - 1.69 (m, 3 H) 1.34 (s, 9 H)

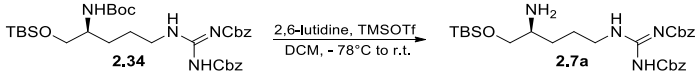
^{13}C NMR (75 MHz, $CDCl_3$) δ = 163.4, 155.9, 153.7, 136.5, 134.4, 128.6, 128.5, 128.3, 128.3, 127.9, 127.8, 68.1, 67.1, 40.4, 28.2. **HRMS (ESI):** calculated for $C_{27}H_{35}N_4O_8$ 543.2449 found 543.2440.



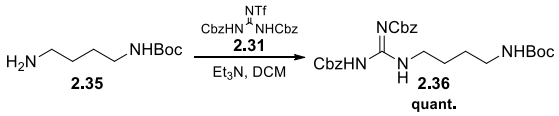
To a solution of **2.32** (1.7 g, 3.13 mmol) and *N*-methyl-morpholine (344 µL, 3.13 mmol) in THF (10 mL) at – 10 °C, isobutyl chloroformate (408 µL, 3.13 mmol) was added dropwise. After 30 min, the reaction was filtered through a celite pad and rinced with THF (1 mL). The filtrate was added to a solution $NaBH_4$ (355 mg, 9.4 mmol) in a mixture H_2O (2 mL) and THF (8 mL) at 0°C. After 4 hours at room temperature, the reaction was quenched with an aqueous solution of HCl (1N) and the resulting mixture was concentrated *in vacuo*. The resulting aqueous solution was extracted with EtOAc three times and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, pentane / AcOEt, 1/1 to 3/7) gave the compound **2.33** (1.22 g, 74 %) as a colourless oil. **$[\alpha]_D$=** – 3.3 ° ($CHCl_3$, c 1.25). **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 11.66 (br. s., 1 H) 8.27 (t, *J*=5.2 Hz, 1 H) 7.11 - 7.37 (m, 10 H) 5.09 (s, 2 H) 5.04 (s, 2 H) 4.80 (d, *J*=7.5 Hz, 1 H) 3.40 - 3.59 (m, 3 H) 3.35 (q, *J*=6.6 Hz, 2 H) 2.75 (br. s., 1 H) 1.42 - 1.64 (m, 3 H) 1.35 (s, 9 H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ = 163.6, 156.0, 153.8, 136.6, 134.5, 128.7, 128.6, 128.4, 128.3, 128.0, 127.9, 68.1, 67.1, 40.8, 28.3, 25.7. **HRMS (ESI):** calculated for $C_{27}H_{37}N_4O_7$ 529.2657 found 529.2648.

To a solution of **2.33** (1.22 g, 2.31 mmol) in DCM (18 mL), imidazole (630 mg, 9.23 mmol) followed by TBSCl (1.39 g, 9.23 mmol) were added at 0 °C. The resulting mixture was stirred at room temperature during 16 hours. The reaction was quenched with an aqueous saturated solution of $NaHCO_3$ and extracted with EtOAC three times. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, pentane / AcOEt, 8/2 to 1/1) gave the compound **2.34** (1.47 g, 99 %) as a colorless oil. **$[\alpha]_D$=** – 5.4 ° ($CHCl_3$, c 1.1). **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 11.72 (s, 1 H) 8.30 (t, *J*=5.2 Hz, 1 H) 7.18 - 7.39 (m, 10 H) 5.12 (s, 2 H) 5.08 (s, 2 H) 4.66 (d, *J*=7.3 Hz, 1 H) 3.47 - 3.62 (m, 3 H) 3.34 - 3.47 (m, 2 H) 1.45 - 1.68 (m, 3 H) 1.40 (s, 9 H) 0.84 (s, 9 H) 0.00 (s, 6 H).

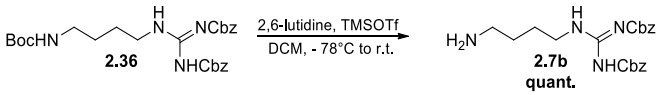
^{13}C NMR (75 MHz, $CDCl_3$) δ = 163.6, 155.8, 155.4, 153.7, 136.7, 128.6, 128.5, 128.3, 128.2, 127.9, 127.7, 67.9, 66.9, 64.6, 40.8, 28.2, 25.7, 18.1, -5.6. **HRMS (ESI):** calculated for $C_{33}H_{51}N_4O_7Si$ 643.3522 found 643.3505.



To a solution of **2.34** (1.47 g, 2.3 mmol) and 2,6-lutidine (2.1 mL, 18.4 mmol) in DCM (23 mL) at – 78 °C, TMSOTf (2.5 mL, 13.8 mmol) was added dropwise and the resulting mixture was allowed to warm to room temperature. After 1 hour, the reaction was quenched with an aqueous saturated solution of $NaHCO_3$ and extracted with EtOAC three times. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, $CHCl_3$ / MeOH (NH_3, 7N), 1/0 to 95/5) gave the compound **2.7a** (1.25 g, 100 %) as a colorless oil. **$[\alpha]_D$**= + 2.1 ° ($CHCl_3$, c 1.1). **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 7.16 - 7.40 (m, 10 H) 5.11 (s, 2 H) 5.06 (s, 2 H) 3.64 (dd, *J*=10.5, 4.0 Hz, 1 H) 3.50 (dd, *J*=10.5, 6.2 Hz, 1 H) 3.32 (t, *J*=6.1 Hz, 2 H) 3.04 - 3.15 (m, 1 H) 1.45 - 1.73 (m, 4 H) 0.82 (s, 9 H) 0.00 (s, 6 H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ = 163.1, 156.1, 153.5, 136.4, 134.4, 128.7, 128.5, 128.3, 128.1, 127.9, 68.1, 67.1, 63.7, 53.0, 40.1, 26.7, 25.6, 24.8, 18.0, -5.8. **HRMS (ESI):** calculated for $C_{28}H_{43}N_4O_5Si$ 543.2997 found 543.2999.

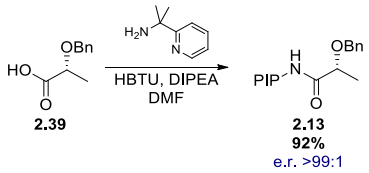


To a solution of *N*-Boc butan-1,4-diamine **2.35** (1 mL, 5.23 mmol) and Et_3N (727 µL, 5.23 mmol) in DCM (20 mL), *N*,*N*'-di-Cbz-*N*''-trifluoromethanesulfonyl-guanidine **2.31** (2.2 g, 4.7 mmol) was added in one portion and the reaction was stirred at room temperature during 16 hours. The reaction was then quenched with an aqueous solution of $NaHSO_4$ (2M) and extracted with DCM three times. The combined organic layers were washed with an aqueous solution of $NaHSO_4$ (2M) and water, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, pentane / AcOEt, 8/2 to 1/1) gave the compound **2.36** (2.34 g, 100 %) as a colourless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 11.65 (s, 1 H) 8.22 (t, *J*=5.4 Hz, 1 H) 7.11 - 7.36 (m, 10 H) 5.04 (s, 2 H) 5.02 (s, 2 H) 4.72 (br. s., 1 H) 3.25 - 3.36 (m, 2 H) 2.93 - 3.08 (m, 2 H) 1.36 - 1.56 (m, 4 H) 1.33 (s, 9 H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ = 163.4, 155.7, 153.5, 136.5, 134.3, 128.5, 128.4, 128.2, 128.1, 127.8, 127.6, 78.7, 67.8, 66.8, 40.4, 39.7, 28.1, 27.0, 26.0.

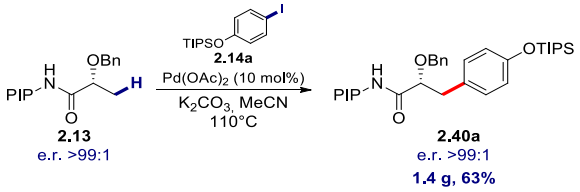


To a solution of **2.36** (1.03 g, 2.07 mmol) and 2,6-lutidine (1.9 mL, 16.53 mmol) in DCM (20 mL) at – 78 °C, TMSOTf (2.3 mL, 12.4 mmol) was added dropwise and the resulting mixture was allowed to warm to room temperature. After 1 hour, the reaction was quenched with an aqueous saturated solution of $NaHCO_3$ and extracted with EtOAC three times. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, $CHCl_3$ / MeOH (NH_3, 7N), 1/0 to 95/5) gave the compound **2.7b** (823 mg, 100 %) as a colorless oil. **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 8.23 (s, 1H), 7.32 - 7.08 (m, 10H), 5.02 (s, 2H), 5.01 (s, 2H), 4.49 (br. s., 2H), 3.36 - 3.21 (m, 2H), 2.54 (t, *J* = 6.8 Hz, 2H), 1.52 - 1.39 (m, 2H), 1.39 - 1.24 (m, 2H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ = 163.7, 155.9, 153.8, 136.8, 134.7, 128.7, 128.6, 128.4, 128.4, 128.1, 127.9, 68.0, 67.0, 41.7, 40.9, 30.8, 26.3.

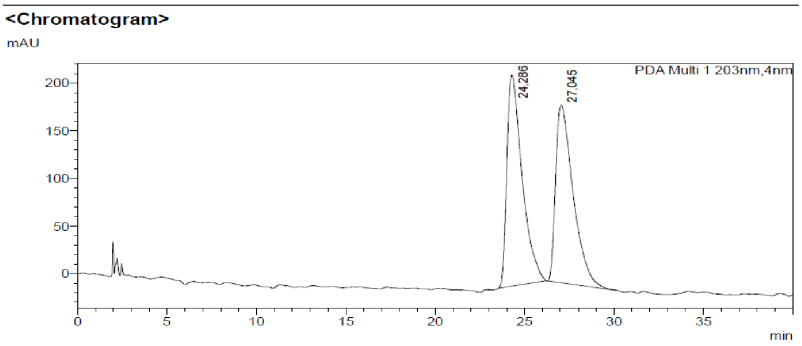
2.4. Synthesis of HPLA fragments



To a solution of (*R*)-2-(benzyloxy)propanoic acid **2.39** (4 g, 22.2 mmol), 2-pyridinylisopropyl (4.5 g, 33.3 mmol), DIPEA (14.7 mL, 89 mmol) in DMF (150 mL) at 0 °C, HBTU (12.6 g, 33.3 mmol) was added in one portion and the resulting mixture was stirred at room temperature during 16 hours. The reaction was then quenched with an aqueous saturated solution of $NaHCO_3$ and extracted three times with ethyl acetate. The combined organic layers were washed three times with water and finally with brine. The organic layer was then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, pentane/ AcOEt, 9/1 to 1/1) gave the compound **2.13** (6 g, 92 %) as a colorless oil. **$[\alpha]_D$**= + 17.8 ° ($CHCl_3$, c 1.3). **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 8.87 (br. s., 1 H) 8.48 - 8.54 (m, 1 H) 7.72 (td, *J*=7.7, 1.9 Hz, 1 H) 7.45 - 7.52 (m, 2 H) 7.31 - 7.42 (m, 4 H) 7.20 (ddd, *J*=7.3, 4.9, 0.9 Hz, 1 H) 4.64 - 4.71 (m, 1 H) 4.57 - 4.64 (m, 1 H) 3.96 (q, *J*=6.8 Hz, 1 H) 1.78 (s, 3 H) 1.78 (s, 3 H) 1.47 (d, *J*=6.8 Hz, 3 H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ = 172.1, 164.2, 147.4, 137.4, 136.8, 128.2, 127.7, 127.6, 121.6, 119.0, 76.9, 71.9, 55.8, 27.4, 27.1, 18.6. **HRMS (ESI):** calculated for $C_{18}H_{23}N_2O_2$ 299.1754 found 299.1763.



A solution of **2.13** (1.2 g, 4.02 mmol), 4-iodophenoxytris(propane-2-yl)silane **2.14a** (6.05 g, 16.1 mmol), $Pd(OAc)_2$ (90 mg, 0.4 mmol) and K_2CO_3 (1.39 g, 10.1 mmol) in MeCN (8 mL) was heated at 110 °C during 24 hours. The cooled mixture was filtered through a pad of celite and concentrated *in vacuo*. Purification by column chromatography (SiO_2, Pentane / EtOAc, 1/0 to 1/1) gave the compound **2.40a** (1.39 g, 63 %) as a slightly brownish oil. $\mathbf{[\alpha]_D}$= + 22 ° ($CHCl_3$, c 1). **HPLC analysis** on a chiral stationary phase (SHIMADZU LC-20AD, Phenomenex Lux Cellulose-1, 5µm 150 x 4,6 mm) showed an *e.e.* > 99% (Hexane/*i*-PrOH : 99.5/0.05 during 40 min; RT (*R*) = 23.1 min; RT (*S*) = 27 min). **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 8.68 (s, 1H), 8.30 (d, *J* = 4.2 Hz, 1H), 7.50 (td, *J* = 7.9, 1.6 Hz, 1H), 7.23 – 7.11 (m, 7H), 7.07 – 6.96 (m, 3H), 6.68 (d, *J* = 8.4 Hz, 2H), 4.44 (d, *J* = 11.3 Hz, 1H), 4.30 (d, *J* = 11.3 Hz, 1H), 3.90 (dd, *J* = 8.0, 3.3 Hz, 1H), 3.07 (dd, *J* = 14.1, 3.2 Hz, 1H), 2.80 (dd, *J* = 14.1, 8.1 Hz, 1H), 1.62 (s, 3H), 1.56 (s, 3H), 1.18 – 1.06 (m, 4H), 0.99 – 0.91 (m, 18H).**^{13}C NMR (75 MHz, $CDCl_3$)** δ = 170.7, 164.3, 154.5, 147.5, 137.5, 136.8, 130.6, 130.2, 128.2, 128.0, 127.7, 121.6, 119.4, 119.1, 81.2, 73.0, 56.1, 38.3, 27.4, 27.3, 17.8, 12.5. **HRMS (ESI):** calculated for $C_{33}H_{46}N_2O_3Si$ 547.3356 found 547.3359.



<Peak Table>

Peak Table

PDA Ch1 203nm

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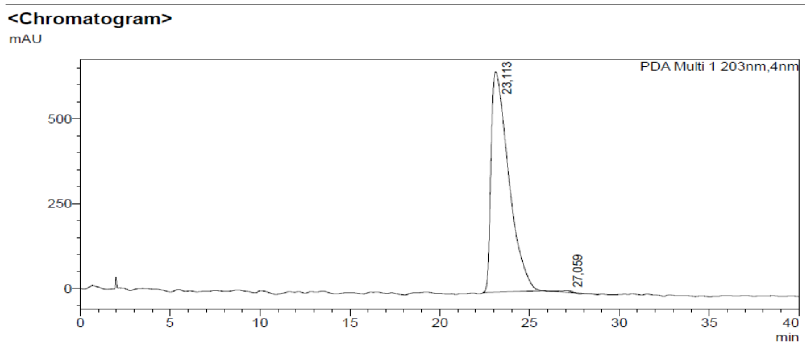

<Peak Table>

Peak Table

PDA Ch1 203nm

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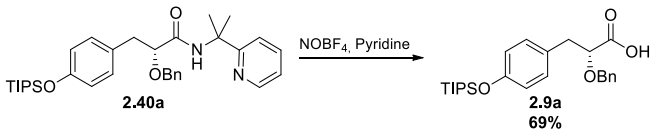
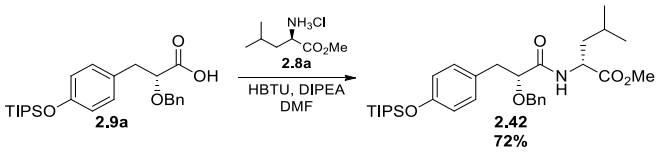
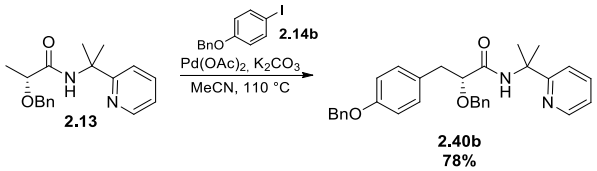


2.40a **2.9a**
69%

To a solution of **2.40a** (400 mg, 0.73 mmol) in pyridine (16 mL) at – 30 °C, $NOBF_4$ (855 mg, 7.32 mmol) was added in one portion and the resulting mixture was stirred 3 hours at – 30 °C then 16 hours at room temperature. The reaction was quenched with an aqueous solution of HCl (6M) until the pH was around 1, then the mixture was extracted with ethyl acetate three time. The combined organic layers were washed with an aqueous solution of HCl (1M) two times, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, pentane / AcOEt / AcOH (1%), 9/1 to 7/3) gave the compound **2.9a** (215 mg, 69 %) as a slightly yellow oil. **$[\alpha]_D$=** +24.2 ° ($CHCl_3$, c 1.4). **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 7.36 – 7.27 (m, 3H), 7.23 – 7.15 (m, 2H), 7.10 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 4.58 (d, *J* = 11.5 Hz, 1H), 4.42 (d, *J* = 11.5 Hz, 1H), 4.16 (dd, *J* = 8.3, 4.0 Hz, 1H), 3.12 (dd, *J* = 14.2, 4.0 Hz, 1H), 2.96 (dd, *J* = 14.2, 8.3 Hz, 1H), 1.31 – 1.18 (m, 3H), 1.10 (m, 18H).**^{13}C NMR (75 MHz, $CDCl_3$)** δ = 155.1, 137.0, 130.6, 129.2, 128.5, 128.1, 128.1, 119.9, 119.7, 79.0, 72.9, 38.4, 18.1, 12.8.**HRMS (ESI):** calculated for $C_{25}H_{36}NaO_4Si$ 451.2281 found 451.2292.

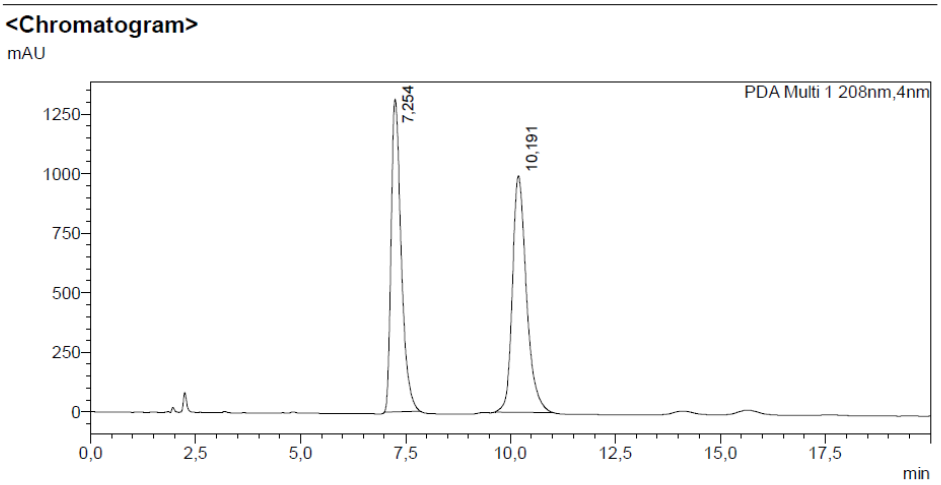


To a solution of **2.9a** (190 mg, 0.44 mmol), D-Leucine methyl ester hydrochloride **2.8a** (121 mg, 0.66 mmol), DIPEA (0.3 mL, 1.8 mmol) in DMF (3 mL) at 0 °C, HBTU (252 mg, 0.66 mmol) was added in one portion and the resulting mixture was stirred at room temperature during 16 hours. The reaction was then quenched with an aqueous saturated solution of $NaHCO_3$ and extracted three times with ethyl acetate. The combined organic layers were washed three times with water and finally with brine. The organic layer was then dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, pentane/ AcOEt, 9/1 to 1/1) gave the compound **2.42** (177 g, 72 %) as a colorless oil. $[\alpha]_D$= + 29 ° ($CHCl_3$, c 1.15). **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 7.29 – 7.13 (m, 5H), 7.01 (d, *J* = 8.5 Hz, 2H), 6.80 (d, *J* = 9.0 Hz, 1H), 6.75 – 6.68 (m, 2H), 4.62 – 4.52 (m, 1H), 4.50 (d, *J* = 11.3 Hz, 1H), 4.32 (d, *J* = 11.3 Hz, 1H), 3.97 (dd, *J* = 7.8, 3.5 Hz, 1H), 3.66 (s, 3H), 3.03 (dd, *J* = 14.2, 3.4 Hz, 1H), 2.77 (dd, *J* = 14.2, 7.8 Hz, 1H), 1.55 – 1.42 (m, 1H), 1.42 – 1.27 (m, 2H), 1.24 – 1.10 (m, 3H), 1.07 – 0.98 (m, 18H), 0.85 – 0.77 (m, 6H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ = 173.4, 171.8, 154.9, 137.2, 130.7, 129.7, 128.6, 128.2, 128.1, 119.7, 81.1, 73.1, 52.3, 50.0, 41.6, 38.4, 24.7, 22.9, 21.8, 18.0, 12.7. **HRMS (ESI):** calculated for $C_{32}H_{50}NO_5Si$ 556.3458 found 556.3453.



A solution of **2.13** (1.5 g, 5.03 mmol), 1-(benzyloxy)-4-iodobenzene **2.14b** (6.24 g, 20.11 mmol), $Pd(OAc)_2$ (113 mg, 0.5 mmol) and K_2CO_3 (1.74 g, 12.6 mmol) in MeCN (10 mL) was heated at 110 °C during 24 hours. The cooled mixture was filtered through a pad of celite and concentrated *in vacuo*. Purification by column chromatography (SiO_2, toluene / Et_2O, 1/0 to 6/4) gave the compound **2.40b** (1.88 g, 78 %) as a slightly brownish oil. $[\alpha]_D$= + 45 ° ($CHCl_3$, c 0.7). **HPLC analysis** on a chiral stationary phase (SHIMADZU LC-20AD, Phenomenex Lux Cellulose-1, 5µm 150 x 4,6 mm) showed an *e.e.* > 99% (Hexane/*i*-PrOH : 90/10 during 20 min; RT (*R*) = 10.19 min; RT (*S*) = 7.25 min).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.64 (s, 1 H), 8.28 - 8.34 (m, 1 H), 7.45 - 7.55 (m, 1 H), 7.06 - 7.32 (m, 13 H), 6.99 (ddd, *J*=7.5, 4.9, 1.0 Hz, 1 H), 6.74 - 6.81 (m, 2 H), 4.89 (s, 2 H), 4.46 (d, *J*=11.4 Hz, 1 H), 4.30 (d, *J*=11.4 Hz, 1 H), 3.89 (dd, *J*=8.1, 3.5 Hz, 1 H), 3.06 (dd, *J*=14.1, 3.5 Hz, 1 H), 2.82 (dd, *J*=14.2, 8.2 Hz, 1 H), 1.62 (s, 3 H), 1.56 (s, 3 H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ = 170.7, 164.2, 157.2, 147.5, 137.3, 137.0, 136.7, 130.6, 130.1, 128.3, 128.1, 127.9, 127.7, 127.6, 127.2, 121.6, 119.0, 114.4, 81.8, 72.9, 69.7, 56.0, 38.2, 27.4, 27.2. **HRMS (ESI):** calculated for $C_{31}H_{33}N_2O_3$ 481.2486 found 481.2477.



<Peak Table>

PDA Ch1 208nm

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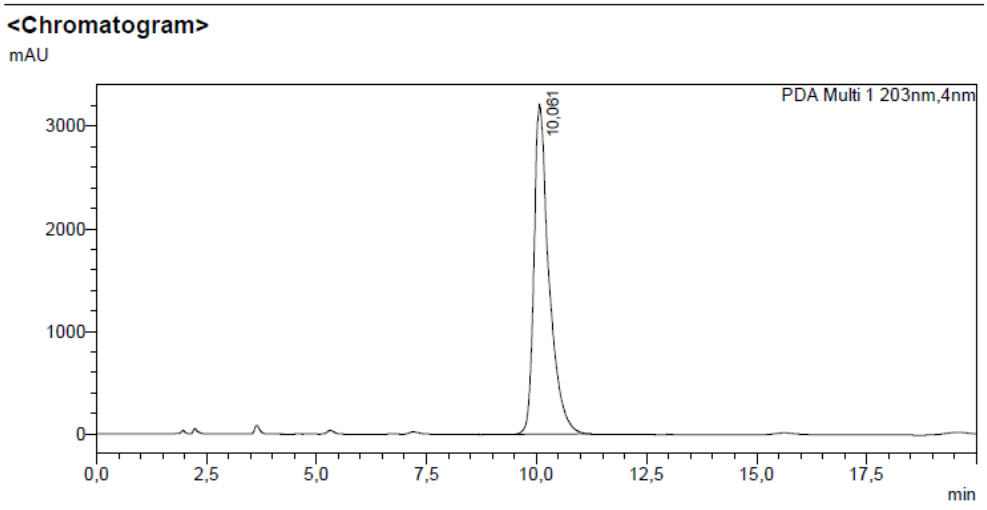

<Peak Table>

PDA Ch1 203nm

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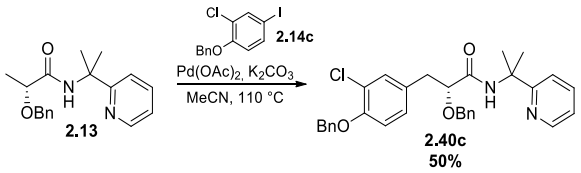
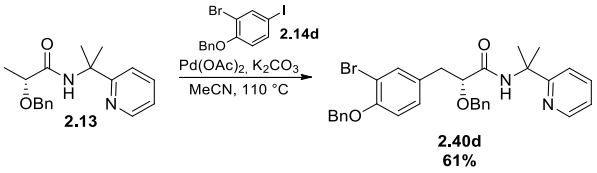
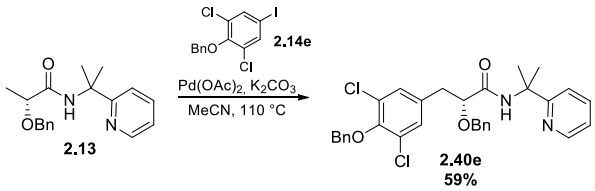


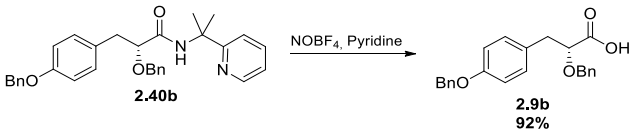
A solution of **2.13** (310 mg, 1.04 mmol), 1-(benzyloxy)-2-chloro-4-iodobenzene **2.14c** (1.43 g, 4.16 mmol), $Pd(OAc)_2$ (23 mg, 0.1 mmol) and K_2CO_3 (360 mg, 2.6 mmol) in MeCN (2 mL) was heated at 110 °C during 24 hours. The cooled mixture was filtered through a pad of celite and concentrated *in vacuo*. Purification by column chromatography (SiO_2, toluene / Et_2O, 1/0 to 6/4) gave the compound **2.40c** (265 mg, 50 %) as a slightly brownish oil. **$[\alpha]_D$**= + 27.9 ° ($CHCl_3$, c 1.1). **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 8.69 (s, 1 H) 8.29 - 8.36 (m, 1 H) 7.52 (td, *J*=7.8, 1.8 Hz, 1 H) 7.27 - 7.36 (m, 2 H) 7.07 - 7.26 (m, 9 H) 6.92 - 7.07 (m, 3 H) 6.72 (d, *J*=8.3 Hz, 1 H) 4.97 (s, 2 H) 4.49 (d, *J*=11.1 Hz, 1 H) 4.31 (d, *J*=11.3 Hz, 1 H) 3.88 (dd, *J*=7.7, 3.6 Hz, 1 H) 3.00 (dd, *J*=14.2, 3.5 Hz, 1 H) 2.80 (dd, *J*=14.2, 7.8 Hz, 1 H) 1.63 (s, 3 H) 1.56 (s, 3 H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ = 170.5, 164.4, 152.8, 147.7, 137.3, 137.0, 136.7, 131.7, 131.5, 129.0, 128.6, 128.5, 128.3, 128.0, 128.0, 127.1, 122.8, 121.9, 119.3, 113.9, 81.6, 73.1, 70.9, 56.3, 38.0, 27.6, 27.4. **HRMS (ESI):** calculated for $C_{31}H_{32}ClN_2O_3$ 515.2096 found 515.2085.



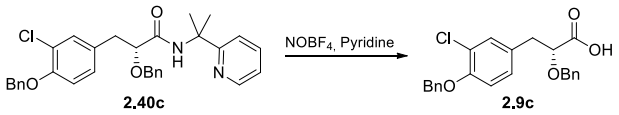
A solution of **2.13** (264 mg, 0.89 mmol), 1-(benzyloxy)-2-bromo-4-iodobenzene **2.14d** (1.38 g, 3.54 mmol), $Pd(OAc)_2$ (20 mg, 0.09 mmol) and K_2CO_3 (306 mg, 2.21 mmol) in MeCN (2 mL) was heated at 110 °C during 24 hours. The cooled mixture was filtered through a pad of celite and concentrated *in vacuo*. Purification by column chromatography (SiO_2, toluene / Et_2O, 1/0 to 6/4) gave the compound **2.40d** (302 mg, 61 %) as a slightly brownish oil. **$[\alpha]_D$**= +25.8 ° ($CHCl_3$, c 1.2). **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 8.76 (s, 1 H) 8.39 - 8.45 (m, 1 H) 7.63 (td, *J*=7.7, 1.8 Hz, 1 H) 7.51 (d, *J*=2.0 Hz, 1 H) 7.40 - 7.46 (m, 2 H) 7.18 - 7.36 (m, 8 H) 7.07 - 7.17 (m, 3 H) 6.79 (d, *J*=8.4 Hz, 1 H) 5.08 (s, 2 H) 4.59 (d, *J*=11.2 Hz, 1 H) 4.40 (d, *J*=11.2 Hz, 1 H) 3.96 (dd, *J*=7.9, 3.5 Hz, 1 H) 3.09 (dd, *J*=14.1, 3.5 Hz, 1 H) 2.89 (dd, *J*=14.2, 7.8 Hz, 1 H) 1.71 (s, 3 H) 1.64 (s, 3 H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ = 170.4, 164.2, 153.5, 147.6, 137.2, 136.9, 136.6, 134.5, 131.8, 129.6, 128.4, 128.3, 128.1, 127.8, 127.8, 126.9, 121.7, 119.1, 113.5, 112.0, 81.4, 73.0, 70.7, 56.1, 37.8, 27.4, 27.3. **HRMS (ESI):** calculated for $C_{31}H_{32}BrN_2O_3$ 559.1591 found 559.1580.



A solution of **2.13** (399.5 mg, 1.34 mmol), 2-(benzyloxy)-1,3-dichloro-5-iodobenzene **2.14e** (2.03 g, 5.36 mmol), $Pd(OAc)_2$ (30 mg, 0.13 mmol) and K_2CO_3 (463 mg, 3.35 mmol) in MeCN (2.7 mL) was heated at 110 °C during 24 hours. The cooled mixture was filtered through a pad of celite and concentrated *in vacuo*. Purification by column chromatography (SiO_2, toluene / Et_2O, 1/0 to 6/4) gave the compound **2.40e** (432 mg, 59 %) as a slightly brownish oil. **$[\alpha]_D$=** +22.8 ° ($CHCl_3$, c 1.3). **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 8.80 (s, 1 H) 8.30 - 8.37 (m, 1 H) 7.53 (td, *J*=7.8, 1.8 Hz, 1 H) 7.37 - 7.45 (m, 2 H) 7.07 - 7.30 (m, 9 H) 6.98 - 7.07 (m, 2 H) 4.83 (s, 2 H) 4.54 (d, *J*=11.3 Hz, 1 H) 4.33 (d, *J*=11.3 Hz, 1 H) 3.90 (dd, *J*=7.3, 3.7 Hz, 1 H) 2.98 (dd, *J*=14.0, 3.7 Hz, 1 H) 2.82 (dd, *J*=14.0, 7.3 Hz, 1 H) 1.64 (s, 3 H) 1.56 (s, 3 H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ = 169.8, 164.0, 149.3, 147.5, 136.9, 136.8, 136.2, 135.3, 130.1, 128.8, 128.3, 128.3, 128.2, 128.0, 127.9, 121.7, 119.0, 80.6, 74.6, 72.9, 56.1, 37.7, 27.3, 27.2. **HRMS (ESI):** calculated for $C_{31}H_{31}Cl_2N_2O_3$ 549.1706 found 549.1693.

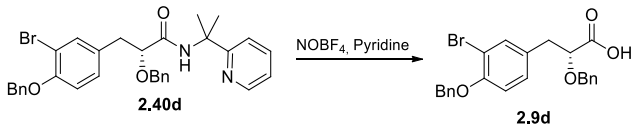


To a solution of **2.40b** (1.8 g, 3.75 mmol) in pyridine (55 mL) at – 30 °C, $NOBF_4$ (4.38 g, 37.5 mmol) was added in one portion and the resulting mixture was stirred 3 hours at – 30 °C then 16 hours at room temperature. The reaction was quenched with an aqueous solution of HCl (6M) until the pH was around 1, then the mixture was extracted with ethyl acetate three time. The combined organic layers were washed with an aqueous solution of HCl (1M) two times, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, pentane / AcOEt / AcOH (1%), 9/1 to 7/3) gave the compound **2.9b** (1.25 g, 92 %) as a slightly yellow oil. **$[\alpha]_D$=** +24.2 ° ($CHCl_3$, c 1.4). **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 11.10 (s,1H), 7.61 - 7.26 (m, 12H), 7.06 (d, *J* = 8.5 Hz, 2H), 5.16 (s, 2H), 4.83 (d, *J* = 11.8 Hz, 1H), 4.54 (d, *J* = 11.8 Hz, 1H), 4.30 (dd, *J* = 8.1, 4.2 Hz, 1H), 3.25 (dd, *J* = 14.1, 4.1 Hz, 1H), 3.16 (dd, *J* = 14.1, 8.3 Hz, 1H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ = 177.8, 157.9, 137.2, 137.1, 130.8, 129.2, 128.7, 128.6, 128.1, 127.6, 114.9, 78.9, 72.8, 70.1, 38.3. **HRMS (ESI):** calculated for $C_{23}H_{22}NaO_4$ 385.1410 found 385.1411.



2.40c **2.9c**

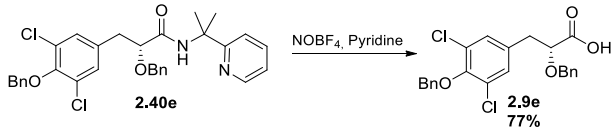
To a solution of **2.40c** (213 mg, 0.41 mmol) in pyridine (8 mL) at – 30 °C, $NOBF_4$ (484 mg, 4.14 mmol) was added in one portion and the resulting mixture was stirred 3 hours at – 30 °C then 16 hours at room temperature. The reaction was quenched with an aqueous solution of HCl (6M) until the pH was around 1, then the mixture was extracted with ethyl acetate three time. The combined organic layers were washed with an aqueous solution of HCl (1M) two times, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, pentane / AcOEt / AcOH (1%), 9/1 to 7/3) gave the compound **2.9c** (125 mg, 76 %) as a slightly yellow oil. **$[\alpha]_D$=** +19.7 ° ($CHCl_3$, c 1). **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 9.70 (br. s., 1 H) 7.32 - 7.40 (m, 2 H) 7.19 - 7.31 (m, 3 H) 7.12 - 7.19 (m, 4 H) 7.03 - 7.10 (m, 2 H) 6.94 (dd, *J*=8.4, 2.2 Hz, 1 H) 6.76 (d, *J*=8.5 Hz, 1 H) 5.02 (s, 2 H) 4.60 (d, *J*=11.7 Hz, 1 H) 4.28 (d, *J*=11.7 Hz, 1 H) 4.01 (dd, *J*=8.4, 4.1 Hz, 1 H) 2.95 (dd, *J*=14.2, 4.1 Hz, 1 H) 2.85 (dd, *J*=14.3, 8.5 Hz, 1 H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ = 177.2, 153.0, 136.6, 136.5, 131.2, 130.2, 128.7, 128.5, 128.3, 128.0, 127.9, 127.9, 127.0, 122.9, 113.9, 78.1, 72.7, 70.8, 37.7. **HRMS (ESI):** calculated for $C_{23}H_{21}ClNaO_4$ 419.1021 found 419.1022.



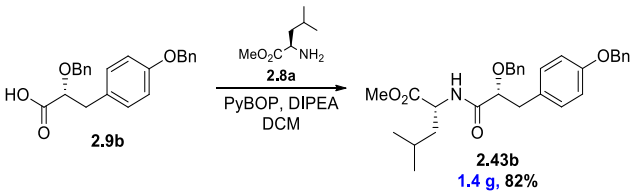
2.40d **2.9d 70%**

To a solution of **2.40d** (290 mg, 0.52 mmol) in pyridine (10 mL) at – 30 °C, $NOBF_4$ (606 mg, 5.2 mmol) was added in one portion and the resulting mixture was stirred 3 hours at – 30 °C then 16 hours at room temperature. The reaction was quenched with an aqueous solution of HCl (6M) until the pH was around 1, then the mixture was extracted with ethyl acetate three time. The combined organic layers were washed with an aqueous solution of HCl (1M) two times, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, pentane / AcOEt / AcOH (1%), 9/1 to 7/3) gave the compound **2.9d** (159 mg, 70 %) as a slightly yellow oil. **$[\alpha]_D$=** + 24.2 ($CHCl_3$, c 1.5). **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 9.13 (br. s., 1 H) 7.32 - 7.41 (m, 3 H) 7.19 - 7.32 (m, 3 H) 7.10 - 7.19 (m, 3 H) 7.05 (dd, *J*=6.5, 2.9 Hz, 2 H) 6.98 (dd, *J*=8.4, 2.0 Hz, 1 H) 6.72 (d, *J*=8.5 Hz, 1 H) 5.01 (s, 2 H) 4.59 (d, *J*=11.7 Hz, 1 H) 4.27 (d, *J*=11.7 Hz, 1 H) 4.00 (dd, *J*=8.5, 4.0 Hz, 1 H) 2.95 (dd, *J*=14.1, 3.8 Hz, 1 H) 2.84 (dd, *J*=14.1, 8.5 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 177.1, 153.8, 136.6, 136.5, 134.2, 130.7, 129.4, 128.5, 128.3, 127.9, 127.9, 127.8, 126.9, 113.6, 112.1, 78.2, 72.6, 70.7, 37.6. **HRMS (ESI):** calculated for $C_{23}H_{21}BrNaO_4$ 463.0515 found 463.0519.

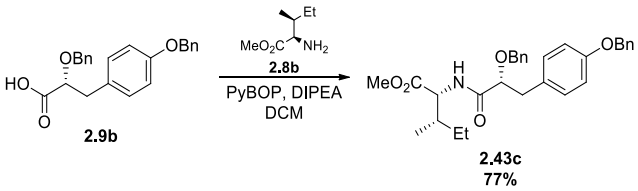


To a solution of **2.40e** (343 mg, 0.62 mmol) in pyridine (12 mL) at – 30 °C, $NOBF_4$ (729 mg, 6.2 mmol) was added in one portion and the resulting mixture was stirred 3 hours at – 30 °C then 16 hours at room temperature. The reaction was quenched with an aqueous solution of HCl (6M) until the pH was around 1, then the mixture was extracted with ethyl acetate three time. The combined organic layers were washed with an aqueous solution of HCl (1M) two times, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, pentane / AcOEt / AcOH (1%), 9/1 to 7/3) gave the compound **2.9e** (208 mg, 77 %) as a slightly yellow oil. **$[\alpha]_D$=** +21.3 ° ($CHCl_3$, c 1.1). **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 8.87 (br. s., 1 H) 7.42 - 7.55 (m, 2 H) 7.24 - 7.38 (m, 3 H) 7.17 - 7.24 (m, 3 H) 7.03 - 7.13 (m, 4 H) 4.94 (s, 2 H) 4.66 (d, *J*=11.7 Hz, 1 H) 4.30 (d, *J*=11.9 Hz, 1 H) 4.03 (dd, *J*=8.7, 3.8 Hz, 1 H) 2.96 (dd, *J*=14.1, 3.8 Hz, 1 H) 2.85 (dd, *J*=14.1, 8.7 Hz, 1 H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ = 176.7, 149.8, 136.4, 136.2, 134.5, 129.9, 129.2, 128.5, 128.4, 128.4, 128.4, 128.2, 128.1, 77.5, 74.9, 72.8, 37.7. **HRMS (ESI):** calculated for $C_{23}H_{20}Cl_2NaO_4$ 453.0631 found 453.0628.

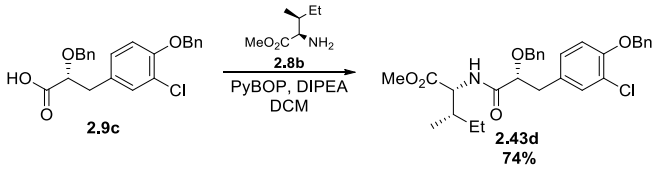


To a solution of **2.9b** (1.25 g, 3.44 mmol) and DIPEA (2.3 mL, 13.74 mmol) in DCM (34 mL) at 0 °C, PyBOP (226 mg, 0.43 mmol) was added in one portion and stirred 20 min at 0 °C. D-Leucine methyl ester hydrochloride **2.8a** (94.6 mg, 0.52 mmol) was then added in one portion at 0 °C. The resulting mixture was stirred at room temperature during 16 hours. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$. The resulting mixture was extracted three times with ethyl acetate and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, pentane/ AcOEt, 9/1 to 1/1) gave the compound **2.43b** (1.384 g, 82 %) as a colorless oil. **$[\alpha]_D$=** + 40.4 ($CHCl_3$, c 1.1).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.14 - 7.37 (m, 10 H) 7.07 (d, *J*=8.7 Hz, 2 H) 6.79 (d, *J*=8.7 Hz, 3 H) 4.93 (s, 2 H) 4.48 - 4.59 (m, 2 H) 4.35 (d, *J*=11.5 Hz, 1 H) 3.97 (dd, *J*=7.2, 3.6 Hz, 1 H) 3.62 (s, 3 H) 3.01 (dd, *J*=14.3, 3.6 Hz, 1 H) 2.80 (dd, *J*=14.2, 7.3 Hz, 1 H) 1.38 - 1.52 (m, 1 H) 1.13 - 1.38 (m, 3 H) 0.77 (d, *J*=6.4 Hz, 3 H) 0.75 (d, *J*=6.4 Hz, 3 H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ = 173.1, 171.5, 157.5, 137.0, 136.9, 130.6, 129.3, 128.4, 128.4, 127.9, 127.9, 127.8, 127.3, 114.4, 80.7, 72.7, 69.8, 52.1, 49.7, 41.2, 37.8, 24.4, 22.7, 21.6. **HRMS (ESI):** calculated for $C_{30}H_{36}NO_5$ 490.2588 found 490.2584.

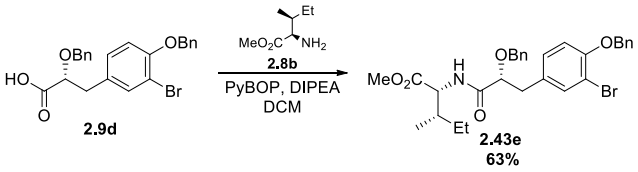


To a solution of **2.9b** (150 mg, 0.41 mmol) and DIPEA (274 µL, 1.66 mmol) in DCM (4 mL) at 0 °C, PyBOP (215 mg, 0.41 mmol) was added in one portion and stirred 20 min at 0 °C. D-*allo*-isoleucine methyl ester hydrochloride[182] **2.8b** (94.6 mg, 0.52 mmol) was then added in one portion at 0 °C. The resulting mixture was stirred at room temperature during 16 hours. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$. The resulting mixture was extracted three times with ethyl acetate and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, pentane/ AcOEt, 9/1 to 1/1) gave the compound **2.43c** (156 mg, 77 %) as a colorless oil. **$[\alpha]_D$=** + 32.7 ($CHCl_3$, c 0.84). **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 7.12 - 7.38 (m, 10 H) 7.08 (m, *J*=8.7 Hz, 2 H) 6.92 (d, *J*=9.4 Hz, 1 H) 6.80 (m, *J*=8.9 Hz, 2 H) 4.95 (s, 2 H) 4.51 - 4.61 (m, 2 H) 4.35 (d, *J*=11.3 Hz, 1 H) 3.98 (dd, *J*=7.4, 3.5 Hz, 1 H) 3.64 (s, 3 H) 3.04 (dd, *J*=14.2, 3.5 Hz, 1 H) 2.80 (dd, *J*=14.2, 7.4 Hz, 1 H) 1.72 - 1.88 (m, 1 H) 1.07 (dd, *J*=13.7, 6.5 Hz, 1 H) 0.82 - 0.94 (m, 1 H) 0.74 - 0.80 (m, 3 H) 0.62 (d, *J*=6.8 Hz, 3 H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ = 172.6, 171.9, 157.7, 137.2, 137.10, 130.8, 129.6, 128.6, 128.5, 128.1, 128.0, 128.0, 127.4, 114.6, 81.1, 72.9, 70.0, 54.7, 52.2, 38.2, 37.5, 26.1, 14.4, 11.8. **HRMS (ESI):** calculated for $C_{30}H_{36}NO_5$ 490.2588 found 490.2580.



To a solution of **2.9c** (115 mg, 0.29 mmol) and DIPEA (191 µL, 1.15 mmol) in DCM (3 mL) at 0 °C, PyBOP (150 mg, 0.29 mmol) was added in one portion and stirred 20 min at 0 °C.

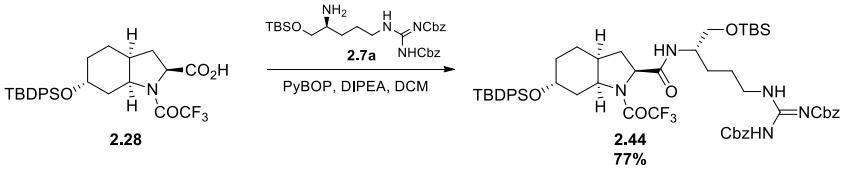
D-*allo*-isoleucine methyl ester hydrochloride **2.8b** (63 mg, 0.35 mmol) was then added in one portion at 0 °C. The resulting mixture was stirred at room temperature during 16 hours. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$. The resulting mixture was extracted three times with ethyl acetate and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, pentane/ AcOEt, 9/1 to 1/1) gave the compound **2.43d** (111 mg, 74 %) as a colorless oil. **$[\alpha]_D$=** + 21.6 ($CHCl_3$, c 0.85). **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 7.14 - 7.42 (m, 11 H) 6.87 - 7.01 (m, 2 H) 6.77 (d, *J*=8.5 Hz, 1 H) 5.05 (s, 2 H) 4.53 - 4.61 (m, 2 H) 4.36 (d, *J*=11.3 Hz, 1 H) 3.96 (dd, *J*=7.2, 3.6 Hz, 1 H) 3.65 (s, 3 H) 2.99 (dd, *J*=14.2, 3.5 Hz, 1 H) 2.77 (dd, *J*=14.2, 7.3 Hz, 1 H) 1.70 - 1.87 (m, 1 H) 1.01 - 1.14 (m, 1 H) 0.82 - 0.93 (m, 1 H) 0.74 - 0.81 (m, 3 H) 0.62 (d, *J*=6.8 Hz, 3 H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ = 172.6, 171.6, 153.1, 136.9, 136.7, 131.7, 130.8, 129.0, 128.7, 128.6, 128.3, 128.2, 128.0, 127.1, 120, 113.9, 80.6, 73.1, 70.9, 54.8, 52.3, 37.8, 37.5, 26.2, 14.4, 11.8. **HRMS (ESI):** calculated for $C_{30}H_{35}ClNO_5$ 524.2198 found 524.2190.



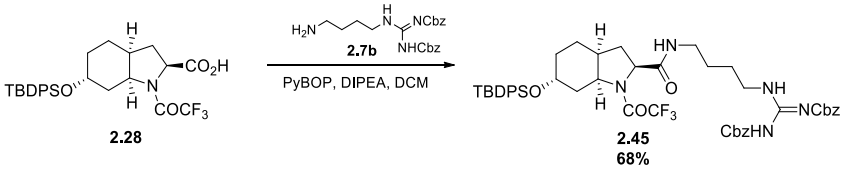
To a solution of **2.9d** (133 mg, 0.3 mmol) and DIPEA (200 µL, 1.21 mmol) in DCM (3 mL) at 0 °C, PyBOP (157 mg, 0.3 mmol) was added in one portion and stirred 20 min at 0 °C. D-*allo*-isoleucine methyl ester hydrochloride **2.8b** (66 mg, 0.36 mmol) was then added in one portion at 0 °C. The resulting mixture was stirred at room temperature during 16 hours. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$. The resulting mixture was extracted three times with ethyl acetate and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, pentane/ AcOEt, 9/1 to 1/1) gave the compound **2.43e** (107 mg, 63 %) as a colorless oil. **$[\alpha]_D$=** + 19.1 ($CHCl_3$, c 0.82). **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 7.35 - 7.43 (m, 3 H) 7.15 - 7.35 (m, 8 H) 7.02 (dd, *J*=8.4, 2.2 Hz, 1 H) 6.93 (d, *J*=9.4 Hz, 1 H) 6.75 (d, *J*=8.5 Hz, 1 H) 5.05 (s, 2 H) 4.54 - 4.62 (m, 2 H) 4.36 (d, *J*=11.5 Hz, 1 H) 3.96 (dd, *J*=7.3, 3.6 Hz, 1 H) 3.65 (s, 3 H) 2.99 (dd, *J*=14.2, 3.5 Hz, 1 H) 2.77 (dd, *J*=14.2, 7.4 Hz, 1 H) 1.74 - 1.88 (m, 1 H) 1.01 - 1.15 (m, 1 H) 0.82 - 0.96 (m, 1 H) 0.74 - 0.82 (m, 3 H) 0.63 (d, *J*=7.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.6, 171.6, 153.9, 136.9, 136.7, 134.7, 131.3, 129.8, 128.7, 128.3, 128.2, 128.0, 127.1, 113.6, 112.3, 80.6, 73.1, 70.9, 54.8, 52.3, 37.8, 37.5, 26.2, 14.4, 11.9. **HRMS (ESI):** calculated for $C_{30}H_{35}BrNO_5$ 568.1693 found 568.1704.

2.5. Fragment coupling and completion of total syntheses

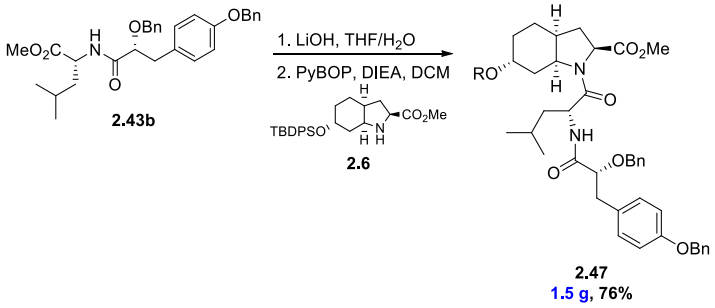


To a solution of **2.28** (226 mg, 0.44 mmol) and DIPEA (220 µL, 1.31 mmol) in DCM (4.5 mL) was added followed by PyBOP (227 mg, 0.44 mmol) at 0 °C. After 30 min at 0 °C, a solution of **2.7a** (260 mg, 0.48 mmol) in DCM (2x2 mL) was added. The resulting mixture was stirred at room temperature during 16 hours. The reaction was then quenched with an aqueous saturated solution of $NaHCO_3$ and extracted with AcOEt three times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, pentane/ AcOEt, 9/1 to 1/1) gave the compound **2.44** (350 mg, 77 %). **$[\alpha]_D$=** – 19.5 ($CHCl_3$, c 1.1). **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 11.76 (s, 1H), 8.36 (t, *J* = 5.6 Hz, 1H), 7.70 – 7.53 (m, 4H), 7.42 – 7.23 (m, 15H), 7.13 (d, *J* = 8.7 Hz, 1H), 5.20 – 4.97 (m, 4H), 4.60 – 4.46 (m, 1H), 4.41 (t, *J* = 8.6 Hz, 1H), 4.07 (s, 1H), 3.99 – 3.82 (m, 1H), 3.71 (dd, *J* = 13.4, 6.6 Hz, 1H), 3.50 (ddd, *J* = 14.7, 10.2, 4.0 Hz, 2H), 3.33 (dd, *J* = 13.5, 5.3 Hz, 1H), 2.32 – 2.15 (m, 2H), 2.14 – 1.64 (m, 4H), 1.64 – 1.50 (m, 3H), 1.51 – 1.38 (m, 3H), 1.38 – 1.29 (m, 1H), 1.07 (s, 9H), 0.85 (s, 9H), -0.00 (s, 6H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ = 169.9, 163.7, 156.5, 156.2 (q, $J_{C\text{-}F}$ = 37 Hz), 153.8, 152.9, 136.8, 135.7, 135.7, 134.7, 134.1, 133.6, 129.8, 129.7, 128.8, 128.7, 128.5, 128.5, 128.1, 128.0, 127.7, 127.6, 116.4 (q, $J_{C\text{-}F}$ = 287 Hz), 68.1, 67.6, 67.1, 64.9, 61.7, 56.4, 51.2, 40.7, 37.3, 33.8, 29.7, 28.8, 27.1, 27.0, 26.3, 26.1, 25.9, 19.4, 19.2, 18.2, -5.5. **^{19}F NMR (282 MHz, $CDCl_3$)** δ = – 70.6. **HRMS (ESI):** calculated for $C_{55}H_{73}F_3N_5O_8Si_2$ 1044.4944 found 1044.4942.



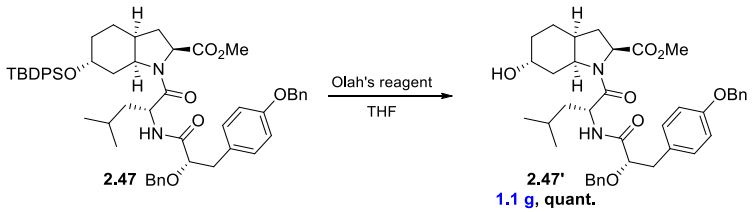
To a solution of **2.28** (262 mg, 0.51 mmol), **2.7b** (436 mg, 1.09 mmol) and DIPEA (668 µL, 4.04 mmol) in DCM (5 mL) was added HBTU (421 mg, 1.11 mmol) at 0 °C. The resulting mixture was stirred at room temperature during 16 hours.

The reaction was then quenched with an aqueous saturated solution of $NaHCO_3$ and extracted with AcOEt three times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, pentane/ AcOEt, 9/1 to 1/1) gave the compound **2.45** (308 mg, 68 %). **$[\alpha]_D$=** – 3.8 ($CHCl_3$, c 1.13). **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 11.66 (s, 1H), 8.28 (t, J = 5.4 Hz, 1H), 7.61 – 7.50 (m, 4H), 7.36 – 7.17 (m, 15H), 6.85 (t, J = 5.5 Hz, 1H), 5.07 (s, 2H), 5.04 (s, 2H), 4.50 – 4.37 (m, 1H), 4.33 (t, J = 8.0 Hz, 1H), 4.01 (s, 1H), 3.46 – 3.25 (m, 2H), 3.17 (dd, J = 11.9, 6.0 Hz, 2H), 2.28 – 2.10 (m, 3H), 1.84 – 1.71 (m, 2H), 1.60 (d, J = 12.0 Hz, 1H), 1.56 – 1.27 (m, 7H), 1.00 (s, 9H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ = (CF_3 coupling are missing) 170.0, 163.7, 156.3, 153.9, 136.8, 135.8, 135.7, 134.7, 134.2, 133.7, 129.9, 129.8, 128.9, 128.8, 128.5, 128.5, 128.2, 128.0, 127.7, 127.7, 68.3, 67.6, 67.2, 61.3, 56.6, 40.6, 39.5, 37.2, 33.7, 28.2, 27.0, 26.7, 26.1, 26.0, 19.5, 19.3. **^{19}F NMR (282 MHz, $CDCl_3$)** δ = – 70.7. **HRMS (ESI):** calculated for $C_{48}H_{56}F_3N_5O_7Si$ 899.3901 found 899.3905.

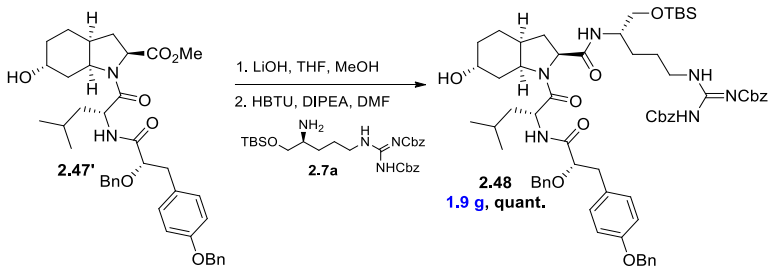


To a solution of **2.43b** (1.07 g, 2.18 mmol) in a mixture of THF (23 mL) and MeOH (7.5 mL), an aqueous solution of LiOH (7.6 mL, 7.57 mmol, 1M) was added dropwise at 0 °C. After 3 hours, the reaction was acidified with an aqueous solution of HCl (1M). The resulting mixture was extracted with DCM three times and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture product was dissolved in DCM (10 mL) and DIPEA (1.1 mL, 6.55 mmol) was added followed by PyBOP (1.15 g, 2.18 mmol) at 0 °C. After 30 min at 0 °C, a solution of **2.6** (1.15 g, 2.62 mmol) in DCM (2x6 mL) was added. The resulting mixture was stirred at room temperature during 16 hours. The reaction was then quenched with an aqueous saturated solution of $NaHCO_3$ and extracted with AcOEt three times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, pentane/ AcOEt, 9/1 to 1/1) gave the compound **2.47** (1.49 g, 76 %) as a colorless oil and as a mixture of conformers (85:15). **$[\alpha]_D$=** + 16.8 ($CHCl_3$, c 1.0).

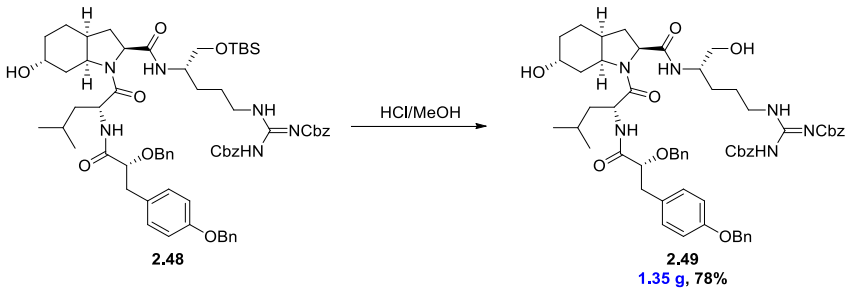
^{1}H NMR (400 MHz, $CDCl_3$, major conformer) δ = 7.60 - 7.71 (m, 4 H) 7.33 - 7.38 (m, 6 H) 7.26 - 7.33 (m, 6 H) 7.14 - 7.25 (m, 7 H) 7.05 - 7.14 (m, 3 H) 6.81 (d, *J*=8.8 Hz, 2 H) 4.96 (s, 2 H) 4.87 (td, *J*=9.9, 3.9 Hz, 1 H) 4.47 (d, *J*=11.0 Hz, 1 H) 4.27 - 4.33 (m, 1 H) 4.23 (d, *J*=11.2 Hz, 1 H) 3.97 (dd, *J*=7.8, 3.7 Hz, 1 H) 3.54 (s, 3 H) 3.06 (dd, *J*=14.2, 3.4 Hz, 1 H) 2.85 (dd, *J*=14.2, 8.1 Hz, 1 H) 2.45 - 2.54 (m, 1 H) 2.35 - 2.45 (m, 1 H) 2.16 - 2.31 (m, 1 H) 2.01 - 2.11 (m, 1 H) 1.81 (td, *J*=12.9, 10.4 Hz, 1 H) 1.61 (t, *J*=11.9 Hz, 1 H) 1.37 - 1.51 (m, 2 H) 1.23 - 1.36 (m, 3 H) 1.04 (s, 9 H) 0.83 (d, *J*=6.4 Hz, 3 H) 0.78 (d, *J*=6.4 Hz, 3 H). **^{13}C NMR (100 MHz, $CDCl_3$, major conformer)** δ = 172.6, 171.0, 170.7, 157.5, 137.1, 137.1, 135.9, 135.8, 134.2, 133.4, 130.7, 129.9, 129.7, 129.6, 128.5, 128.4, 128.3, 127.8, 127.8, 127.7, 127.6, 127.4, 114.4, 81.1, 72.8, 69.9, 67.4, 59.2, 54.8, 52.0, 48.0, 42.6, 38.3, 37.2, 34.3, 30.2, 29.6, 27.1, 25.9, 24.4, 23.4, 22.0, 19.2. **HRMS (ESI):** calculated for $C_{55}H_{67}N_2O_7Si$ 895.4712 found 895.4703.



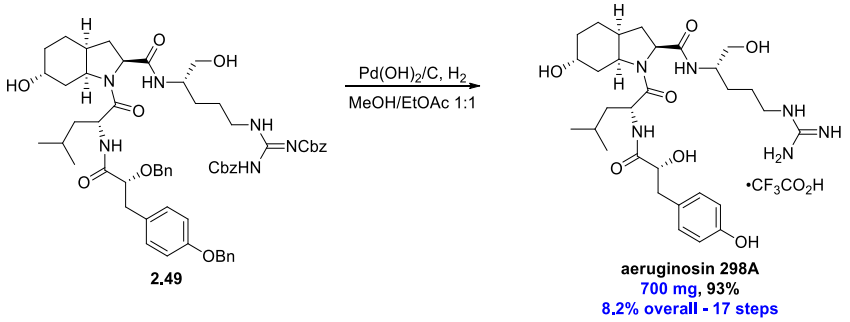
To a solution of **2.47** (1.49 g, 1.66 mmol) in THF (10 mL), Olah's reagent (HF•pyridine, 7/3) (10 mL) was added in plastic tube at 0 °C. After 16 hours at room temperature, the reaction was quenched with an aqueous saturated solution of $NaHCO_3$ and the resulting mixture was extracted with $CHCl_3$ three times. The combined organic layers were washed with an aqueous saturated solution of $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, $CHCl_3$ / MeOH, 1/0 to 97/3) gave the compound **2.47'** (1.08 g, 99 %) as a colorless oil. **$[\alpha]_D$=** + 12.1 ($CHCl_3$, c 3.7). **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 8.5 (d, *J*=3.7 Hz, 1 H) 7.10 - 7.40 (m, 10 H) 7.07 (d, *J*=8.7 Hz, 2 H) 6.80 (d, *J*=8.7 Hz, 2 H) 4.95 (s, 2 H) 4.79 (td, *J*=9.5, 4.1 Hz, 1 H) 4.46 (d, *J*=11.3 Hz, 1 H) 4.13 - 4.39 (m, 3 H) 4.06 - 4.12 (m, 1 H) 3.94 (dd, *J*=7.5, 3.6 Hz, 1 H) 3.59 (s, 3 H) 3.00 (dd, *J*=14.1, 3.4 Hz, 1 H) 2.78 (dd, *J*=14.2, 7.6 Hz, 1 H) 2.30 - 2.43 (m, 1 H) 2.18 - 2.30 (m, 1 H) 2.03 - 2.17 (m, 2 H) 1.81 - 1.94 (m, 1 H) 1.65 - 1.72 (m, 1 H) 1.34 - 1.64 (m, 7 H) 0.84 (d, *J*=5.8 Hz, 3 H) 0.78 (d, *J*=6.0 Hz, 3 H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ = 172.8, 171.3, 170.3, 157.6, 149.7, 137.2, 137.1, 130.8, 129.7, 128.6, 128.5, 128.4, 127.9, 127.5, 114.5, 80.8, 72.9, 70.0, 65.4, 59.1, 54.5, 52.1, 48.1, 42.6, 38.2, 37.2, 34.2, 30.4, 25.8, 24.5, 23.5, 21.9, 19.3. **HRMS (ESI):** calculated for $C_{39}H_{48}N_2NaO_7$ 679.3354 found 679.3373.



To a solution of **2.47'** (1.08 g, 1.65 mmol) in a mixture of THF (9 mL) and MeOH (4.6 mL), an aqueous solution of LiOH (5 mL, 5 mmol, 1M) was added dropwise at 0 °C. After 3 hours, the reaction was acidified with an aqueous solution of HCl (1M). The resulting mixture was extracted with DCM three times and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture product was dissolved in DMF (8 mL) and DIPEA (0.8 mL, 5 mmol) was added followed by a solution of **2.7a** (1.07 g, 2 mmol) in DMF (8 mL). To the resulting mixture at 0 °C, HBTU (750 mg, 2 mmol) was added in one portion and stirred at room temperature during 16 hours. The reaction was then quenched with an aqueous saturated solution of $NaHCO_3$ and extracted with AcOEt three times. The combined organic layers were washed with water three times and one time with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, $CHCl_3$ / MeOH, 1/0 to 98/2) gave the compound **2.48** (1.93 g, 100 %) as a colorless oil. $\mathbf{[\alpha]_D}$= + 7.2 ($CHCl_3$, c 3.3). **^{1}H NMR (500 MHz, $CDCl_3$)** δ = 11.71 (s, 1 H) 8.37 (t, *J*=5.6 Hz, 1 H) 7.26 - 7.47 (m, 16 H) 7.17 - 7.26 (m, 4 H) 7.14 (m, *J*=8.5 Hz, 2 H) 6.87 (m, *J*=8.5 Hz, 2 H) 6.84 (d, *J*=9.2 Hz, 1 H) 5.13 (dd, *J*=7.8, 3.5 Hz, 4 H) 5.02 (s, 2 H) 4.73 - 4.81 (m, 1 H) 4.60 (d, *J*=11.3 Hz, 1 H) 4.39 (d, *J*=11.6 Hz, 1 H) 4.32 - 4.37 (m, 1 H) 4.23 (dt, *J*=11.4, 5.8 Hz, 1 H) 4.18 (br. s., 1 H) 4.03 (dd, *J*=7.2, 3.5 Hz, 1 H) 3.92 - 4.01 (m, 1 H) 3.59 (dd, *J*=9.9, 3.8 Hz, 1 H) 3.44 - 3.52 (m, 2 H) 3.23 - 3.32 (m, 1 H) 3.08 (dd, *J*=14.2, 3.5 Hz, 1 H) 2.88 (dd, *J*=14.2, 7.2 Hz, 1 H) 2.20 - 2.35 (m, 5 H) 2.13 - 2.19 (m, 1 H) 1.97 - 2.04 (m, 1 H) 1.81 - 1.91 (m, 1 H) 1.50 - 1.70 (m, 7 H) 1.40 - 1.50 (m, 1 H) 1.25 - 1.36 (m, 2 H) 0.94 (d, *J*=5.8 Hz, 3 H) 0.89 (s, 9 H) 0.87 (d, *J*=6.1 Hz, 3 H) 0.04 (s, 6 H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 171.5, 171.1, 170.8, 163.7, 157.6, 156.0, 153.6, 137.1, 137.1, 136.8, 134.6, 130.7, 129.5, 128.7, 128.7, 128.5, 128.4, 128.4, 128.3, 128.1, 127.9, 127.4, 114.4, 80.8, 77.3, 77.0, 76.8, 72.7, 69.9, 68.0, 67.0, 65.8, 65.0, 60.3, 54.7, 50.5, 48.5, 41.9, 40.8, 37.9, 36.7, 33.7, 29.7, 27.8, 25.8, 25.6, 25.6, 24.4, 23.4, 21.7, 19.3, 18.23, -5.4, -5.5. **HRMS (ESI):** calculated for $C_{66}H_{87}N_6O_{11}Si$ 1167.6197 found 1167.6149.

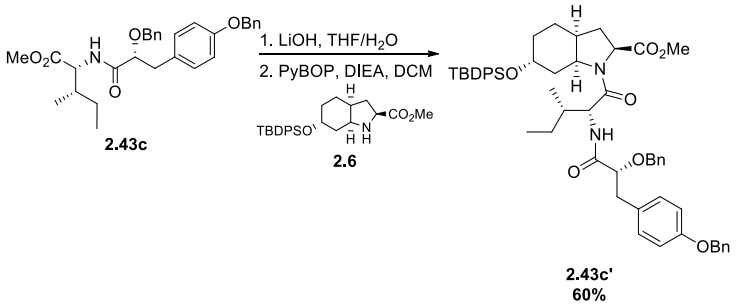


The compound **2.48** (1.925 g, 1.65 mmol) was dissolved in $CHCl_3$ (10 mL) at 0 °C, then a cooled solution of HCl / MeOH (0.5 %, 50 mL) was added slowly and the reaction was stirred 2 hours at 0 °C. The reaction was quenched with an aqueous saturated solution of $NaHCO_3$ and extracted with AcOEt three times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, $CHCl_3$ / MeOH, 95/5) gave the compound **2.49** (1.355 g, 78 %) as a colorless oil. **$[\alpha]_D$=** + 2.5 ($CHCl_3$, c 1.8). **^{1}H NMR (500 MHz, $CDCl_3$)** δ = 11.76 (br. s., 1 H) 8.37 (t, *J*=5.5 Hz, 1 H) 7.44 - 7.48 (m, 2 H) 7.26 - 7.44 (m, 16 H) 7.16 (m, *J*=8.9 Hz, 2 H) 6.91 (m, *J*=8.5 Hz, 2 H) 6.87 (d, *J*=5.8 Hz, 1 H) 6.78 (d, *J*=8.9 Hz, 1 H) 5.17 (s, 2 H) 5.14 (s, 2 H) 5.05 (s, 2 H) 4.65 (d, *J*=11.6 Hz, 1 H) 4.43 - 4.51 (m, 2 H) 4.31 - 4.37 (m, 1 H) 4.18 - 4.26 (m, 2 H) 4.05 (dd, *J*=7.2, 3.5 Hz, 1 H) 3.91 - 4.00 (m, 1 H) 3.58 - 3.72 (m, 2 H) 3.42 - 3.53 (m, 4 H) 3.09 (dd, *J*=14.3, 3.4 Hz, 1 H) 2.86 (dd, *J*=14.2, 7.2 Hz, 1 H) 2.49 (dt, *J*=13.8, 4.2 Hz, 1 H) 2.28 - 2.41 (m, 2 H) 2.12 - 2.24 (m, 1 H) 2.00 - 2.11 (m, 2 H) 1.93 (br. s., 1 H) 1.55 - 1.70 (m, 5 H) 1.19 - 1.42 (m, 5 H) 0.90 (d, *J*=2.7 Hz, 3 H) 0.89 (d, *J*=2.7 Hz, 3 H). **^{13}C NMR (126 MHz, $CDCl_3$)** δ = 173.8, 171.7, 171.5, 163.7, 157.7, 156.0, 153.8, 137.1, 137.0, 136.8, 134.6, 130.7, 129.2, 128.7, 128.6, 128.6, 128.5, 128.4, 128.1, 128.0, 127.9, 127.9, 127.4, 114.5, 80.7, 73.0, 70.0, 68.1, 67.1, 65.7, 64.0, 60.9, 54.8, 51.4, 50.3, 41.0, 39.9, 38.1, 36.8, 33.3, 30.5, 29.7, 27.8, 26.3, 25.9, 24.6, 23.3, 21.3, 19.1. **HRMS (ESI):** calculated for $C_{60}H_{73}N_6O_{11}$ 1053.5332 found 1053.5300.



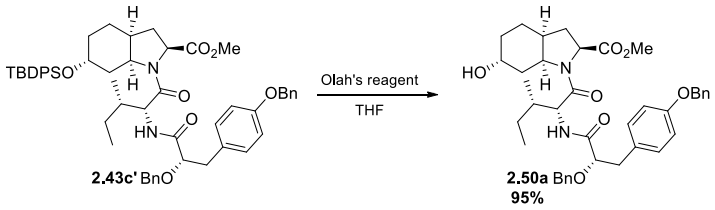
The compound **2.49** (1.1 g, 1.04 mmol) was dissolved in a mixture of AcOEt (22 mL) and MeOH (22 mL) and $Pd(OH)_2/C$ (20 %) (3.67 g, 5.22 mmol) was added in one portion.

The atmosphere was replaced by hydrogen (1 atm.) by three cycles of vacuum / H_2. After 6 hours, the resulting mixture was filtered through a pad of celite and rinced with EtOAc (200 mL) followed by MeOH (200 mL). The filtrate was concentrated *in vacuo*. The crude mixture was dissolved in MeOH (4 mL) then TFA (0.6 mL) was added at 0°C. Purification by column chromatography (C18, H_2O / MeCN / 1% TFA, 9/1 to 1/1) gave aeruginosin 298A as TFA salt (700 mg, 93 %) as a white amorphous solid and as a mixture of conformers (85:15). **$[\alpha]_D$=** + 17.3 ° (H_2O, c 1.2), Lit.[71] **$[\alpha]_D$=** + 22.3 ° (H_2O, c 0.36). **^{1}H NMR (400 MHz, DMSO d_6, major conformer)** δ = 7.56 (d, *J* = 8.6 Hz, 1H), 7.52 (t, *J* = 5.7 Hz, 1H), 7.46 (d, *J* = 8.3 Hz, 1H), 6.98 (d, *J* = 8.5 Hz, 2H), 6.63 (d, *J* = 8.5 Hz, 2H), 4.57 – 4.45 (m, 1H), 4.16 (t, *J* = 8.9 Hz, 1H), 4.08 – 3.96 (m, 2H), 3.91 (br. s, 1H), 3.69 – 3.57 (m, 1H), 3.30 (dd, *J* = 10.7, 5.0 Hz, 1H), 3.21 (dd, *J* = 10.7, 6.2 Hz, 1H), 3.12 – 2.99 (m, 2H), 2.85 (dd, *J* = 14.0, 3.4 Hz, 1H), 2.63 (dd, *J* = 13.9, 7.5 Hz, 1H), 2.36 – 2.18 (m, 1H), 2.12 – 1.92 (m, 3H), 1.88 – 1.73 (m, 1H), 1.65 (t, *J* = 13.0 Hz, 1H), 1.60 – 1.24 (m, 10H), 1.20 (t, *J* = 11.1 Hz, 1H), 0.87 (d, *J* = 6.4 Hz, 3H), 0.81 (d, *J* = 6.4 Hz, 3H). **^{13}C NMR (101 MHz, DMSO d_6, major conformer)** δ = 172.85, 171.31, 169.76, 158.54 (q, $J_{C\text{-}F}$ = 36.0 Hz), 156.75, 155.78, 130.48, 128.12, 115.88 (q, $J_{C\text{-}F}$ = 292.1 Hz), 114.70, 72.15, 63.89, 63.30, 59.92, 54.02, 50.20, 48.10, 41.90, 40.80, 39.39, 36.02, 33.50, 30.54, 28.00, 26.03, 25.08, 23.98, 23.40, 21.39, 19.00 (2 C). **HRMS (ESI):** calculated for $C_{30}H_{49}N_6O_7$ 605.3657 found 605.3646.



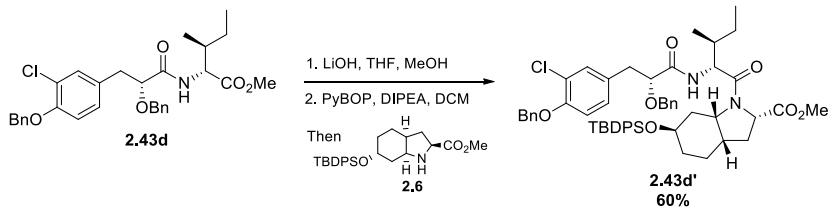
To a solution of **2.43c** (148 mg, 0.30 mmol) in a mixture of THF (3.1 mL) and MeOH (1.0 mL), an aqueous solution of LiOH (1.0 mL, 1.0 mmol, 1M) was added dropwise at 0 °C. After 3 hours, the reaction was acidified with an aqueous solution of HCl (1M). The resulting mixture was extracted with DCM three times and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture product was dissolved in DCM (3 mL) and DIPEA (150 µL, 0.90 mmol) was added followed by PyBOP (157 mg, 0.30 mmol) at 0 °C. After 30 min at 0 °C, a solution of **2.6** (159 mg, 0.36 mmol) in DCM (1 mL) was added. The resulting mixture was stirred at room temperature during 16 hours. The reaction was then quenched with an aqueous saturated solution of $NaHCO_3$ and extracted with AcOEt three times.

The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, pentane/ AcOEt, 9/1 to 1/1) gave the compound **2.43c'** (161 mg, 60 %) as a colorless oil. **$[\alpha]_D$=** + 7.8 ($CHCl_3$, c 1.1). **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.56 - 7.73 (m, 4 H) 7.07 - 7.39 (m, 18 H) 6.81 (d, *J*=8.7 Hz, 2 H) 4.96 (s, 2 H) 4.72 (dd, *J*=9.4, 5.7 Hz, 1 H) 4.46 (d, *J*=11.1 Hz, 1 H) 4.27 - 4.40 (m, 2 H) 4.19 (d, *J*=11.1 Hz, 1 H) 4.02 (br. s., 1 H) 3.95 (dd, *J*=8.2, 3.3 Hz, 1 H) 3.53 (s, 3 H) 3.08 (dd, *J*=14.1, 3.2 Hz, 1 H) 2.83 (dd, *J*=14.2, 8.2 Hz, 1 H) 2.34 - 2.49 (m, 2 H) 2.17 – 2.31 (m, 1H) 2.00 - 2.13 (m, 1 H) 1.74 - 1.90 (m, 2 H) 1.50 - 1.66 (m, 2 H) 1.44 (d, *J*=14.3 Hz, 1 H) 1.28 – 1.34 (m, 1H) 1.06 (s, 9 H) 0.82 (t, *J*=7.2 Hz, 3 H) 0.70 (d, *J*=6.6 Hz, 3 H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ = 172.8, 171.3, 170.0, 157.6, 137.3, 137.3, 136.0, 135.8, 134.4, 133.3, 130.8, 130.2, 129.8, 129.7, 128.6, 128.5, 128.4, 127.9, 127.9, 127.8, 127.7, 127.5, 114.6, 81.5, 72.9, 70.0, 67.6, 59.2, 54.8, 53.7, 52.1, 38.8, 38.7, 37.3, 34.4, 30.3, 29.7, 27.2, 26.6, 26.2, 19.4, 14.0, 12.2. **HRMS (ESI):** calculated for $C_{55}H_{67}N_2O_7Si$ 895.4712 found 895.4714.

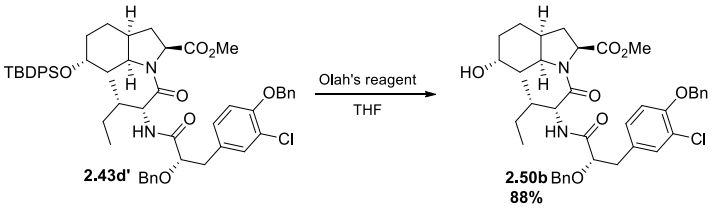


To a solution of **2.43c'** (147 mg, 0.164 mmol) in THF (2 mL), Olah's reagent (HF•pyridine, 7/3) (2 mL) was added in plastic tube at 0 °C. After 16 hours at room temperature, the reaction was quenched with an aqueous saturated solution of $NaHCO_3$ and the resulting mixture was extracted with $CHCl_3$ three times. The combined organic layers were washed with an aqueous saturated solution of $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, $CHCl_3$ / MeOH, 1/0 to 97/3) gave the compound **2.50a** (102 mg, 95%) as a colorless oil. **$[\alpha]_D$=** + 7.3 ($CHCl_3$, c 1.1). **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 7.13 - 7.39 (m, 10 H) 7.09 (m, *J*=8.8 Hz, 2 H) 6.81 (m, *J*=8.8 Hz, 2 H) 4.97 (s, 2 H) 4.60 (dd, *J*=9.9, 7.2 Hz, 1 H) 4.45 (d, *J*=11.0 Hz, 1 H) 4.31 (dd, *J*=10.0, 8.1 Hz, 1 H) 4.25 (dd, *J*=11.9, 6.0 Hz, 1 H) 4.21 (d, *J*=11.0 Hz, 1 H) 4.10 (br. s., 1 H) 3.93 (dd, *J*=8.1, 3.4 Hz, 1 H) 3.58 (s, 3 H) 3.08 (br. s., 1 H) 3.02 (dd, *J*=14.2, 3.4 Hz, 1 H) 2.78 (dd, *J*=14.2, 8.1 Hz, 1 H) 2.55 (br. s., 1 H) 2.38 (dq, *J*=12.6, 6.1 Hz, 1 H) 2.17 - 2.28 (m, 1 H) 2.06 - 2.17 (m, 2 H) 1.90 (td, *J*=12.8, 10.3 Hz, 1 H) 1.66 - 1.79 (m, 1 H) 1.53 - 1.64 (m, 1 H) 1.37 - 1.53 (m, 2 H) 1.14 - 1.29 (m, 1 H) 0.92 - 1.07 (m, 1 H) 0.82 (t, *J*=7.3 Hz 3 H) 0.69 (d, *J*=6.6 Hz, 3 H).

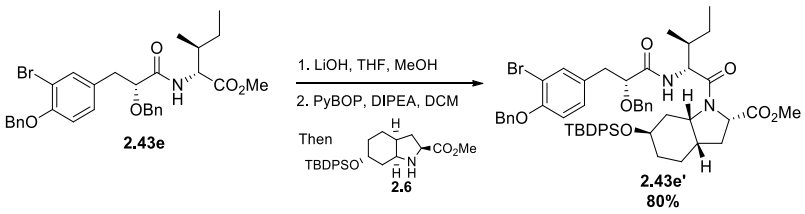
^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.8, 171.6, 169.7, 157.5, 137.1, 136.9, 130.7, 129.7, 128.5, 128.4, 128.3, 127.8, 127.4, 114.5, 81.1, 72.9, 69.9, 65.5, 58.9, 54.4, 53.6, 52.1, 38.5, 38.4, 37.2, 34.0, 30.3, 25.9, 25.6, 19.2, 14.1, 11.8. **HRMS (ESI):** calculated for $C_{49}H_{49}N_2O_7$ 657.3534 found 657.3535.



To a solution of **2.43d** (103 mg, 0.20 mmol) in a mixture of THF (2 mL) and MeOH (0.7 mL), an aqueous solution of LiOH (0.7 mL, 0.7 mmol, 1M) was added dropwise at 0 °C. After 3 hours, the reaction was acidified with an aqueous solution of HCl (1M). The resulting mixture was extracted with DCM three times and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture product was dissolved in DCM (2 mL) and DIPEA (97 µL, 0.59 mmol) was added followed by PyBOP (102 mg, 0.20 mmol) at 0 °C. After 30 min at 0 °C, a solution of **2.6** (103 mg, 0.23 mmol) in DCM (1 mL) was added. The resulting mixture was stirred at room temperature during 16 hours. The reaction was then quenched with an aqueous saturated solution of $NaHCO_3$ and extracted with AcOEt three times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, pentane/ AcOEt, 9/1 to 1/1) gave the compound **2.43d'** (161 mg, 60 %) as a colorless oil. **$[\alpha]_D$**= + 4.2 ($CHCl_3$, c 0.88). **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.59 - 7.73 (m, 4 H) 7.12 - 7.43 (m, 18 H) 7.00 (dd, *J*=8.4, 2.2 Hz, 1 H) 6.78 (d, *J*=8.5 Hz, 1 H) 5.06 (s, 2 H) 4.72 (dd, *J*=9.4, 5.7 Hz, 1 H) 4.49 (d, *J*=11.1 Hz, 1 H) 4.27 - 4.40 (m, 2 H) 4.20 (d, *J*=11.3 Hz, 1 H) 3.93 (dd, *J*=8.0, 3.5 Hz, 1 H) 3.54 (s, 3 H) 3.02 (dd, *J*=14.1, 3.4 Hz, 1 H) 2.81 (dd, *J*=14.2, 8.0 Hz, 1 H) 2.34 - 2.47 (m, 2 H) 2.17 - 2.33 (m, 1 H) 2.01 - 2.14 (m, 1 H) 1.73 - 1.92 (m, 2 H) 1.51 - 1.66 (m, 2 H) 1.45 (d, *J*=16.4 Hz, 1 H) 1.21 - 1.34 (m, 3 H) 1.06 (s, 9 H) 0.82 (t, *J*=7.1 Hz, 3 H) 0.69 (d, *J*=6.8 Hz, 3 H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ = 172.9, 171.0, 170.1, 153.0, 137.1, 136.8, 136.1, 135.9, 134.5, 133.4, 131.7, 131.4, 129.9, 129.8, 129.0, 128.7, 128.5, 128.0, 128.0, 127.7, 127.2, 122.9, 114.0, 81.0, 73.1, 71.0, 67.7, 59.3, 54.9, 53.8, 52.2, 38.9, 38.3, 37.4, 34.4, 30.4, 27.3, 26.7, 26.2, 19.7, 19.4, 14.0, 12.3. **HRMS (ESI):** calculated for $C_{55}H_{66}ClN_2O_7Si$ 929.4322 found 929.4302.

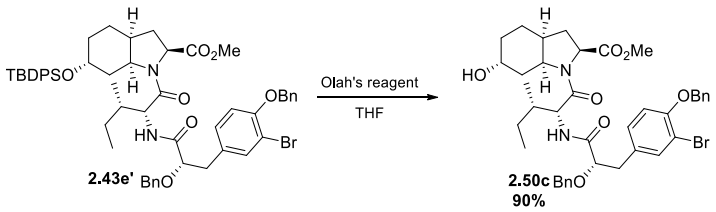


To a solution of **2.43d'** (136 mg, 0.146 mmol) in THF (2 mL), Olah's reagent (HF•pyridine, 7/3) (2 mL) was added in plastic tube at 0 °C. After 16 hours at room temperature, the reaction was quenched with an aqueous saturated solution of $NaHCO_3$ and the resulting mixture was extracted with $CHCl_3$ three times. The combined organic layers were washed with an aqueous saturated solution of $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, $CHCl_3$ / MeOH, 1/0 to 97/3) gave the compound **2.50b** (89 mg, 88 %) as a colorless oil. **$[\alpha]_D$=** + 4.6 ($CHCl_3$, c 0.81). **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.36 - 7.42 (m, 2 H) 7.28 - 7.34 (m, 2 H) 7.12 - 7.27 (m, 8 H) 6.96 (dd, *J*=8.4, 2.1 Hz, 1 H) 6.78 (d, *J*=8.6 Hz, 1 H) 5.06 (s, 2 H) 4.60 (dd, *J*=10.0, 7.1 Hz, 1 H) 4.48 (d, *J*=11.0 Hz, 1 H) 4.31 (dd, *J*=10.0, 8.1 Hz, 1 H) 4.22 (d, *J*=11.2 Hz, 2 H) 4.11 (br. s., 1 H) 3.91 (dd, *J*=8.1, 3.4 Hz, 1 H) 3.59 (s, 3 H) 2.99 (br. s., 1 H) 2.97 (dd, *J*=14.3, 3.3 Hz, 1 H) 2.76 (dd, *J*=14.3, 7.9 Hz, 1 H) 2.46 (br. s., 1 H) 2.38 (dq, *J*=12.6, 6.3 Hz, 1 H) 2.17 - 2.27 (m, 1 H) 2.06 - 2.17 (m, 2 H) 1.90 (td, *J*=12.8, 10.3 Hz, 1 H) 1.68 - 1.78 (m, 1 H) 1.53 - 1.64 (m, 1 H) 1.39 - 1.53 (m, 2 H) 1.14 - 1.27 (m, 1 H) 0.92 - 1.06 (m, 1 H) 0.80 - 0.86 (m, 3 H) 0.68 (d, *J*=6.6 Hz, 3 H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ = 172.8, 171.3, 169.6, 152.9, 136.7, 136.6, 131.5, 130.9, 128.8, 128.5, 128.4, 128.0, 127.9, 127.0, 122.8, 113.8, 80.5, 73.0, 70.8, 65.5, 58.9, 54.4, 53.6, 52.1, 38.5, 38.0, 37.2, 34.0, 30.3, 26.0, 25.6, 19.2, 14.1, 11. **HRMS (ESI):** calculated for $C_{39}H_{48}ClN_2O_7$ 691.3145 found 691.3129.



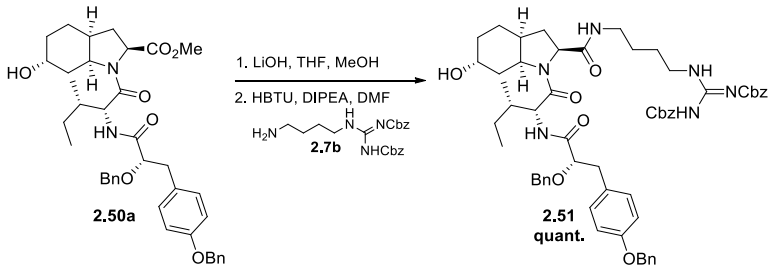
To a solution of **2.43e** (99 mg, 0.175 mmol) in a mixture of THF (2 mL) and MeOH (0.6 mL), an aqueous solution of LiOH (0.6 mL, 0.61 mmol, 1M) was added dropwise at 0 °C. After 3 hours, the reaction was acidified with an aqueous solution of HCl (1M). The resulting mixture was extracted with DCM three times and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture product was dissolved in DCM (2 mL) and DIPEA (87 µL, 0.52 mmol) was added followed by PyBOP (91 mg, 0.175 mmol) at 0 °C.

After 30 min at 0 °C, a solution of **2.6** (92 mg, 0.21 mmol) in DCM (1 mL) was added. The resulting mixture was stirred at room temperature during 16 hours. The reaction was then quenched with an aqueous saturated solution of $NaHCO_3$ and extracted with AcOEt three times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, pentane/ AcOEt, 9/1 to 1/1) gave the compound **2.43e'** (136 mg, 80 %) as a colorless oil. **$[\alpha]_D$=** + 5.2 ($CHCl_3$, c 1.21). **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 7.59 - 7.71 (m, 4 H) 7.13 - 7.46 (m, 18 H) 7.05 (dd, *J*=8.3, 2.1 Hz, 1 H) 6.75 (d, *J*=8.5 Hz, 1 H) 5.06 (s, 2 H) 4.72 (dd, *J*=9.5, 5.7 Hz, 1 H) 4.49 (d, *J*=11.1 Hz, 1 H) 4.27 - 4.40 (m, 2 H) 4.20 (d, *J*=11.1 Hz, 1 H) 3.94 (d, *J*=3.6 Hz, 1 H) 3.55 (s, 3 H) 3.03 (dd, *J*=14.3, 3.4 Hz, 1 H) 2.80 (dd, *J*=14.2, 8.0 Hz, 1 H) 2.33 - 2.49 (m, 2 H) 2.15 - 2.33 (m, 1 H) 2.07 (td, *J*=13.3, 6.4 Hz, 1 H) 1.83 (td, *J*=12.8, 10.5 Hz, 1 H) 1.50 - 1.72 (m, 3 H) 1.45 (d, *J*=13.8 Hz, 1 H) 1.22 - 1.36 (m, 3 H) 1.03 - 1.09 (m, 9 H) 0.83 (t, *J*=7.3 Hz, 3 H) 0.70 (d, *J*=6.8 Hz, 3 H). **^{13}C NMR (100 MHz, $CDCl_3$)** δ = 172.9, 171.0, 170.1, 153.9, 137.1, 136.8, 136.1, 135.9, 134.7, 134.5, 133.4, 131.9, 129.9, 129.8, 128.7, 128.7, 128.5, 128.0, 128.0, 128.0, 127.7, 127.1, 113.7, 112.2, 81.1, 73.1, 71.0, 67.7, 59.3, 54.9, 53.8, 52.2, 38.9, 38.2, 37.4, 34.4, 30.4, 29.8, 27.3, 26.7, 26.2, 19.7, 19.4, 14.1, 12.3. **HRMS (ESI):** calculated for $C_{55}H_{66}BrN_2O_7Si$ 973.3817 found 973.3807.



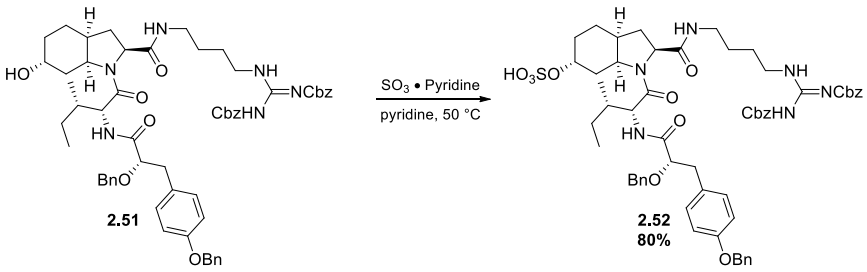
To a solution of **28e'** (123 mg, 0.126 mmol) in THF (2 mL), Olah's reagent (HF•pyridine, 7/3) (2 mL) was added in plastic tube at 0 °C. After 16 hours at room temperature, the reaction was quenched with an aqueous saturated solution of $NaHCO_3$ and the resulting mixture was extracted with $CHCl_3$ three times. The combined organic layers were washed with an aqueous saturated solution of $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, $CHCl_3$ / MeOH, 1/0 to 97/3) gave the compound **43c** (84 mg, 90 %) as a colorless oil. **$[\alpha]_D$=** + 1.6 ($CHCl_3$, c 0.78).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36 - 7.44 (m, 3 H) 7.27 - 7.35 (m, 2 H) 7.13 - 7.27 (m, 7 H) 7.02 (dd, *J*=8.4, 2.1 Hz, 1 H) 6.75 (d, *J*=8.3 Hz, 1 H) 5.06 (s, 2 H) 4.60 (dd, *J*=9.8, 7.1 Hz, 1 H) 4.47 (d, *J*=11.2 Hz, 1 H) 4.32 (dd, *J*=10.0, 8.3 Hz, 1 H) 4.22 (d, *J*=11.0 Hz, 1 H) 4.11 (br. s., 1 H) 3.91 (dd, *J*=8.1, 3.4 Hz, 1 H) 3.59 (s, 3 H) 2.97 (dd, *J*=14.3, 3.3 Hz, 1 H) 2.92 (br. s., 1 H) 2.75 (dd, *J*=14.2, 8.1 Hz, 1 H) 2.33 - 2.45 (m, 1 H) 2.30 (br. s., 1 H) 2.17 - 2.26 (m, 1 H) 2.06 - 2.17 (m, 2 H) 1.90 (td, *J*=12.8, 10.3 Hz, 1 H) 1.67 - 1.79 (m, 1 H) 1.53 - 1.66 (m, 2 H) 1.38 - 1.53 (m, 2 H) 1.13 - 1.28 (m, 1 H) 0.92 - 1.08 (m, 1 H) 0.79 - 0.87 (m, 3 H) 0.68 (d, *J*=6.6 Hz, 3 H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 173.0, 171.5, 170.0, 153.9, 136.9, 136.8, 134.7, 131.6, 129.8, 128.7, 128.7, 128.6, 128.2, 128.0, 127.1, 113.7, 112.3, 80.8, 73.2, 71.0, 65.7, 59.1, 54.6, 53.8, 52.3, 38.6, 38.1, 37.3, 34.2, 30.4, 26.2, 25.8, 19.3, 14.3, 12.0. **HRMS (ESI):** calculated for $C_{39}H_{48}BrN_2O_7$ 735.2639 found 735.2627.

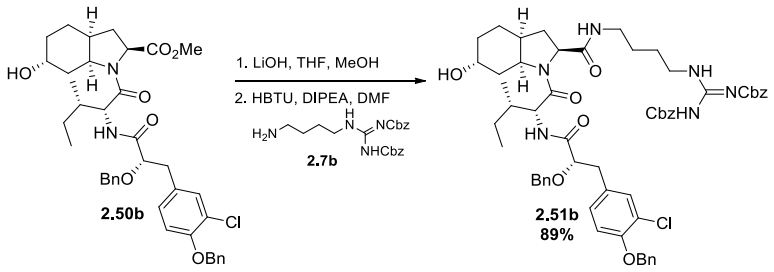


To a solution of **2.50a** (63 mg, 0.096 mmol) in a mixture of THF (0.5 mL) and MeOH (0.25 mL), an aqueous solution of LiOH (0.29 mL, 0.29 mmol, 1M) was added dropwise at 0 °C. After 3 hours, the reaction was acidified with an aqueous solution of HCl (1M). The resulting mixture was extracted with DCM three times and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture product was dissolved in DMF (1 mL) and DIPEA (48 µL, 0.29 mmol) was added followed by a solution of **2.7b** (46 mg, 0.12 mmol) in DMF (1 mL). To the resulting mixture at 0 °C, HBTU (44 mg, 0.12 mmol) was added in one portion and stirred at room temperature during 16 hours. The reaction was then quenched with an aqueous saturated solution of $NaHCO_3$ and extracted with AcOEt three times. The combined organic layers were washed with water three times and one time with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, pentane/ AcOEt, 7/3 to 1/9) gave the compound **2.51** (98.6 mg, 100 %) as a colorless oil. **$[\alpha]_D$=** -3.4 ($CHCl_3$, c 0.9).

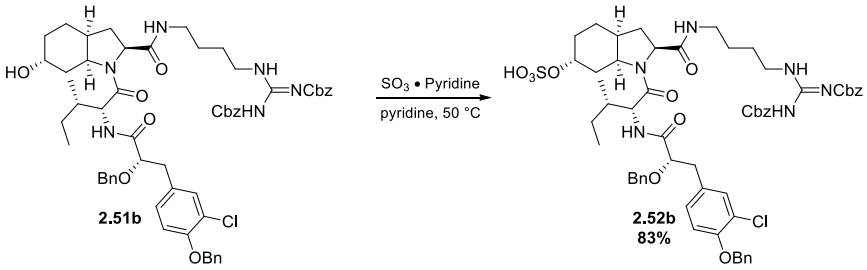
^{1}H NMR (300 MHz, $CDCl_3$) δ = 11.62 (s, 1 H) 8.19 (t, *J*=5.4 Hz, 1 H) 7.10 - 7.40 (m, 20 H) 6.99 - 7.10 (m, 3 H) 6.92 (t, *J*=5.6 Hz, 1 H) 6.79 (d, *J*=8.6 Hz, 2 H) 5.04 (s, 2 H) 5.02 (s, 2 H) 4.93 (s, 2 H) 4.41 - 4.49 (m, 2 H) 4.30 - 4.36 (m, 1 H) 4.26 (d, *J*=11.2 Hz, 1 H) 4.15 - 4.23 (m, 1 H) 4.07 (br. s., 1 H) 3.91 (dd, *J*=7.6, 3.4 Hz, 1 H) 3.25 (q, *J*=6.0 Hz, 2 H) 3.16 (dq, *J*=13.1, 6.5 Hz, 1 H) 2.96 - 3.07 (m, 2 H) 2.88 (br. s., 1 H) 2.77 (dd, *J*=14.2, 7.6 Hz, 1 H) 1.94 - 2.24 (m, 5 H) 1.33 - 1.64 (m, 10 H) 0.93 - 1.06 (m, 1 H) 0.81 (t, *J*=7.3 Hz, 3 H) 0.67 (d, *J*=6.8 Hz, 3 H). **^{13}C NMR (75 MHz, $CDCl_3$)** δ = 172.1, 171.5, 170.5, 163.7, 157.6, 156.0, 153.8, 137.1, 137.0, 136.8, 134.6, 130.8, 129.6, 128.8, 128.7, 128.6, 128.5, 128.4, 128.4, 128.1, 128.1, 128.0, 127.9, 127.4, 114.6, 81.0, 72.8, 70.0, 68.1, 67.1, 65.7, 60.0, 55.0, 54.2, 40.7, 39.1, 38.2, 37.6, 36.6, 33.4, 29.7, 29.4, 26.5, 26.3, 26.1, 19.3, 14.3, 11.9. **HRMS (ESI):** calculated for $C_{59}H_{71}N_6O_{10}$ 1023.5226 found 1023.5215.



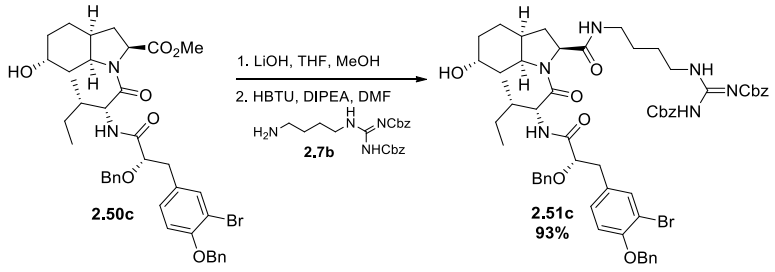
In a test tube, **2.51** (103.2 mg, 0.1 mmol) was dissolved in pyridine (3.6 mL) and SO_3•pyridine complex (69 mg, 0.43 mmol) was added in one portion and stirred at 50 °C during 3 hours. To the resulting mixture, water was added and the reaction was extracted with EtOAc three times. The combined organic layers were washed with an aqueous solution of HCl (1N) two times, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, $CHCl_3$ / MeOH, 9/1) gave the compound **2.52** (89.1 mg, 80 %) as a colorless oil. **$[\alpha]_D$=** -2.7 ($CHCl_3$, c 0.6). **^{1}H NMR (300 MHz, DMSO-*d*$_6$)** δ = 11.59 (s, 1 H) 8.38 (t, *J*=5.6 Hz, 1 H) 7.82 (t, *J*=5.4 Hz, 1 H) 7.18 - 7.48 (m, 20 H) 7.13 (d, *J*=8.8 Hz, 2 H) 6.91 (d, *J*=8.6 Hz, 2 H) 5.19 (s, 2 H) 5.06 (s, 2 H) 5.03 (s, 2 H) 4.45 - 4.54 (m, 2 H) 4.35 - 4.44 (m, 2 H) 4.21 (t, *J*=8.9 Hz, 1 H) 4.05 (dd, *J*=7.1, 4.2 Hz, 1 H) 3.22 - 3.31 (m, 1 H) 3.00 - 3.08 (m, 2 H) 2.98 (d, *J*=2.9 Hz, 1 H) 2.80 - 2.89 (m, 1 H) 2.23 - 2.38 (m, 2 H) 1.96 - 2.09 (m, 2 H) 1.92 (d, *J*=12.2 Hz, 1 H) 1.71 - 1.86 (m, 2 H) 1.51 - 1.65 (m, 2 H) 1.33 - 1.51 (m, 6 H) 1.15 - 1.27 (m, 1 H) 0.92 - 1.04 (m, 1 H) 0.83 - 0.90 (m, 3 H) 0.68 (d, *J*=6.6 Hz, 3 H). **^{13}C NMR (101 MHz, DMSO-*d*$_6$)** δ = 171.3, 170.5, 169.0, 163.1, 157.0, 155.0, 152.7, 137.6, 137.3, 136.9, 135.13, 130.5, 128.6, 128.4, 128.3, 128.1, 128.0, 127.7, 127.6, 114.3, 80.3, 79.2, 71.3, 69.1, 67.6, 66.3, 60.0, 54.0, 53.0, 40.2, 38.1, 37.3, 37.1, 36.0, 31.6, 30.6, 29.0, 26.2, 25.8, 23.3, 19.4, 14.0, 11.8. **HRMS (ESI):** calculated for $C_{59}H_{71}N_6O_{13}S$ 1103.4794 found 1103.4755.



To a solution of **2.50b** (66 mg, 0.095 mmol) in a mixture of THF (0.5 mL) and MeOH (0.25 mL), an aqueous solution of LiOH (0.28 mL, 0.28 mmol, 1M) was added dropwise at 0 °C. After 3 hours, the reaction was acidified with an aqueous solution of HCl (1M). The resulting mixture was extracted with DCM three times and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture product was dissolved in DMF (1 mL) and DIPEA (47 µL, 0.28 mmol) was added followed by a solution of **2.7b** (45 mg, 0.11 mmol) in DMF (1 mL). To the resulting mixture at 0 °C, HBTU (43 mg, 0.11 mmol) was added in one portion and stirred at room temperature during 16 hours. The reaction was then quenched with an aqueous saturated solution of $NaHCO_3$ and extracted with AcOEt three times. The combined organic layers were washed with water three times and one time with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, pentane/ AcOEt, 7/3 to 1/9) gave the compound **2.51b** (88.5 mg, 89 %) as a colorless oil. **$[\alpha]_D$=** – 1.3 ($CHCl_3$, c 0.78). **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 11.69 (s, 1 H) 8.26 (t, *J*=5.4 Hz, 1 H) 7.40 - 7.49 (m, 2 H) 7.18 - 7.40 (m, 18 H) 7.11 (d, *J*=8.6 Hz, 1 H) 6.98 - 7.02 (m, 1 H) 6.94 - 6.98 (m, 1 H) 6.82 (d, *J*=8.6 Hz, 1 H) 5.12 (s, 2 H) 5.09 (s, 4 H) 4.56 (d, *J*=11.2 Hz, 1 H) 4.51 (dd, *J*=8.4, 6.5 Hz, 1 H) 4.32 - 4.42 (m, 2 H) 4.25 (dt, *J*=11.1, 5.3 Hz, 1 H) 4.14 (br. s., 1 H) 3.97 (dd, *J*=7.2, 3.5 Hz, 1 H) 3.28 - 3.36 (m, 2 H) 3.23 (dq, *J*=13.1, 6.4 Hz, 1 H) 3.11 (dt, *J*=12.8, 6.4 Hz, 1 H) 3.01 (dd, *J*=14.3, 3.5 Hz, 1 H) 2.82 (dd, *J*=14.2, 7.3 Hz, 1 H) 2.24 - 2.33 (m, 2 H) 2.15 - 2.24 (m, 2 H) 1.99 - 2.09 (m, 1 H) 1.72 (t, *J*=12.2 Hz, 1 H) 1.55 - 1.67 (m, 4 H) 1.42 - 1.55 (m, 5 H) 1.16 - 1.31 (m, 3 H) 0.98 - 1.12 (m, 1 H) 0.88 (t, *J*=7.2 Hz, 3 H) 0.73 (d, *J*=6.8 Hz, 3 H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 171.7, 171.5, 170.5, 163.7, 156.0, 153.8, 153.0, 136.9, 136.7, 134.7, 131.6, 130.8, 129.0, 128.8, 128.7, 128.6, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 128.0, 127.1, 122.9, 113.9, 80.5, 72.9, 70.9, 68.1, 67.1, 65.7, 60.0, 55.0, 54.1, 40.7, 39.1, 37.8, 37.7, 36.7, 33.5, 29.4, 26.5, 26.4, 26.2, 25.8, 19.3, 14.3, 11.9. **HRMS (ESI):** calculated for $C_{59}H_{70}ClN_6O_{10}$ 1057.4836 found 1057.4834.

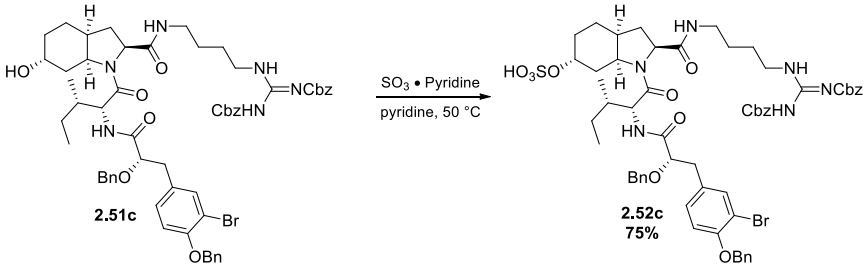


In a test tube, **2.51b** (87 mg, 0.083 mmol) was dissolved in pyridine (3 mL) and SO_3•pyridine complex (56 mg, 0.35 mmol) was added in one portion and stirred at 50 °C during 3 hours. To the resulting mixture, water was added and the reaction was extracted with EtOAc three times. The combined organic layers were washed with an aqueous solution of HCl (1N) two times, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, $CHCl_3$ / MeOH, 9/1) gave the compound **2.52b** (77.5 mg, 83 %) as a colorless oil. **$[\alpha]_D$=** – 0.06 ($CHCl_3$, c 3.88). **^{1}H NMR (400 MHz, DMSO-*d*$_6$, major rotamer)** δ = 11.59 (br. s., 1 H) 8.38 (t, *J*=5.5 Hz, 1 H) 8.33 (s, 1 H) 7.84 (t, *J*=5.5 Hz, 1 H) 7.20 - 7.50 (m, 21 H) 7.05 - 7.18 (m, 2 H) 5.19 (s, 2 H) 5.17 (s, 2 H) 5.03 (s, 2 H) 4.53 (d, *J*=6.1 Hz, 1 H) 4.47 - 4.51 (m, 1 H) 4.37 - 4.45 (m, 2 H) 4.21 (t, *J*=8.9 Hz, 1 H) 4.00 - 4.10 (m, 2 H) 3.27 (q, *J*=6.5 Hz, 2 H) 2.96 - 3.10 (m, 3 H) 2.81 - 2.90 (m, 1 H) 2.23 - 2.36 (m, 2 H) 1.97 - 2.09 (m, 2 H) 1.92 (d, *J*=12.5 Hz, 1 H) 1.72 - 1.87 (m, 2 H) 1.54 - 1.62 (m, 1 H) 1.31 - 1.52 (m, 6 H) 1.17 (dd, *J*=13.6, 6.5 Hz, 1 H) 0.95 (td, *J*=14.3, 6.8 Hz, 1 H) 0.83 - 0.89 (m, 3 H) 0.67 (d, *J*=6.6 Hz, 3 H). **^{13}C NMR (101 MHz, DMSO-*d*$_6$, major rotamer)** δ = 171.3, 170.3, 168.9, 163.1, 155.1, 152.7, 152.2, 137.6, 136.9, 136.8, 135.1, 130.9, 130.9, 129.3, 128.6, 128.5, 128.4, 128.3, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.4, 127.3, 121.0, 113.9, 79.8, 71.2, 69.9, 67.6, 66.3, 60.0, 54.0, 52.9, 40.2, 38.1, 37.3, 36.5, 36.0, 31.7, 30.6, 26.2, 25.8, 23.3, 19.4, 13.9, 11.8. **HRMS (ESI):** calculated for $C_{59}H_{70}ClN_6O_{13}S$ 1137.4405 found 1137.4361.



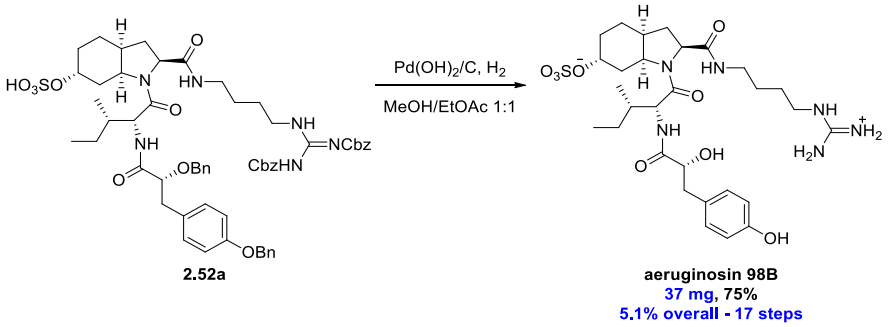
To a solution of **2.50c** (57.5 mg, 0.078 mmol) in a mixture of THF (0.4 mL) and MeOH (0.2 mL), an aqueous solution of LiOH (0.23 mL, 0.23 mmol, 1M) was added dropwise at 0 °C. After 3 hours, the reaction was acidified with an aqueous solution of HCl (1M). The resulting mixture was extracted with DCM three times and the combined organic layers were dried over

$MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture product was dissolved in DMF (0.8 mL) and DIPEA (39 µL, 0.23 mmol) was added followed by a solution of **2.7b** (37 mg, 0.094 mmol) in DMF (1 mL). To the resulting mixture at 0 °C, HBTU (35.6 mg, 0.094 mmol) was added in one portion and stirred at room temperature during 16 hours. The reaction was then quenched with an aqueous saturated solution of $NaHCO_3$ and extracted with AcOEt three times. The combined organic layers were washed with water three times and one time with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, pentane/ AcOEt, 7/3 to 1/9) gave the compound **2.51c** (83 mg, 96 %) as a colorless oil. **$[\alpha]_D$=** – 3 ($CHCl_3$, c 0.88). **^{1}H NMR (400 MHz, $CDCl_3$)** δ = 11.63 (s, 1 H) 8.19 (t, *J*=5.4 Hz, 1 H) 7.34 - 7.45 (m, 3 H) 7.11 - 7.34 (m, 17 H) 7.03 (d, *J*=8.6 Hz, 1 H) 6.99 (dd, *J*=8.3, 2.0 Hz, 1 H) 6.90 (t, *J*=5.9 Hz, 1 H) 6.74 (d, *J*=8.3 Hz, 1 H) 5.06 (s, 2 H) 5.03 (s, 2 H) 5.03 (s, 2 H) 4.49 (d, *J*=11.5 Hz, 1 H) 4.43 (dd, *J*=8.6, 6.6 Hz, 1 H) 4.25 - 4.36 (m, 2 H) 4.14 - 4.23 (m, 1 H) 4.08 (br. s., 1 H) 3.90 (dd, *J*=7.2, 3.5 Hz, 1 H) 3.21 - 3.30 (m, 2 H) 3.11 - 3.21 (m, 1 H) 3.00 - 3.11 (m, 1 H) 2.94 (dd, *J*=14.3, 3.3 Hz, 1 H) 2.75 (dd, *J*=14.2, 7.3 Hz, 1 H) 2.47 (br. s., 2 H) 2.17 - 2.29 (m, 2 H) 1.97 - 2.17 (m, 4 H) 1.66 (t, *J*=12.1 Hz, 1 H) 1.36 - 1.60 (m, 8 H) 1.10 - 1.24 (m, 3 H) 0.91 - 1.05 (m, 1 H) 0.79 - 0.84 (m, 3 H) 0.67 (d, *J*=6.8 Hz, 3 H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 171.7, 171.5, 170.5, 163.8, 156.0, 153.9, 153.9, 136.9, 136.7, 134.7, 131.2, 129.8, 128.9, 128.8, 128.7, 128.6, 128.5, 128.5, 128.2, 128.2, 128.0, 127.1, 113.6, 112.2, 80.6, 72.9, 70.9, 68.2, 67.2, 65.8, 60.0, 55.1, 54.2, 40.7, 39.1, 37.7, 36.7, 33.6, 29.8, 29.4, 26.6, 26.4, 26.3, 25.8, 19.4, 14.3, 12.0. **HRMS (ESI):** calculated for $C_{59}H_{70}BrN_6O_{10}$ 1101.4331 found 1101.4318.



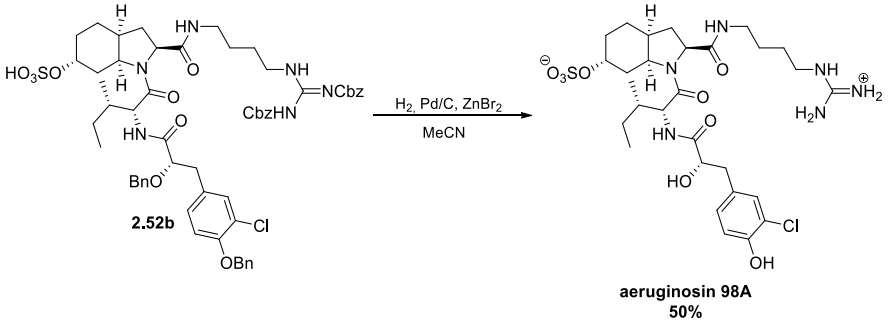
In a test tube, **2.51c** (82 mg, 0.074 mmol) was dissolved in pyridine (2.6 mL) and SO_3•pyridine complex (51 mg, 0.32 mmol) was added in one portion and stirred at 50 °C during 3 hours. To the resulting mixture, water was added and the reaction was extracted with EtOAc three times. The combined organic layers were washed with an aqueous solution of HCl (1N) two times, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2, $CHCl_3$ / MeOH, 9/1) gave the compound **2.52c** (66 mg, 75 %) as a colorless oil. **$[\alpha]_D$=** – 23.7 ($CHCl_3$, c 0.47).

^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.59 (s, 1 H) 8.38 (t, *J*=5.7 Hz, 1 H) 8.33 (s, 1 H) 7.83 (t, *J*=5.5 Hz, 1 H) 7.44 - 7.52 (m, 3 H) 7.21 - 7.44 (m, 17 H) 7.00 - 7.20 (m, 2 H) 5.19 (s, 2 H) 5.17 (s, 2 H) 5.03 (s, 2 H) 4.44 - 4.56 (m, 2 H) 4.36 - 4.44 (m, 2 H) 4.20 (t, *J*=8.9 Hz, 1 H) 3.99 - 4.14 (m, 2 H) 3.26 (q, *J*=6.5 Hz, 2 H) 2.95 - 3.09 (m, 3 H) 2.79 - 2.90 (m, 1 H) 2.24 - 2.37 (m, 2 H) 1.95 - 2.08 (m, 2 H) 1.91 (d, *J*=12.7 Hz, 1 H) 1.70 - 1.86 (m, 2 H) 1.52 - 1.64 (m, 1 H) 1.29 - 1.52 (m, 7 H) 1.10 - 1.21 (m, 1 H) 0.89 - 1.01 (m, 1 H) 0.81 - 0.89 (m, 3 H) 0.67 (d, *J*=6.6 Hz, 3 H). **^{13}C NMR (101 MHz, DMSO-d_6)** δ = 171.3, 170.2, 168.9, 163.0, 155.0, 153.0, 152.7, 137.6, 136.9, 136.8, 135.1, 133.9, 131.4, 130.0, 128.6, 128.5, 128.4, 128.3, 128.2, 128.2, 128.0, 127.8, 127.7, 127.6, 127.3, 127.2, 113.8, 110.7, 79.8, 71.2, 71.1, 69.9, 67.6, 66.3, 60.0, 54.0, 52.9, 40.2, 38.1, 37.3, 36.4, 36.0, 31.7, 30.6, 29.0, 26.2, 25.8, 23.3, 19.4, 13.9, 11.8. **HRMS (ESI):** calculated for $C_{59}H_{70}BrN_6O_{13}S$ 1181.3899 found 1181.3854.

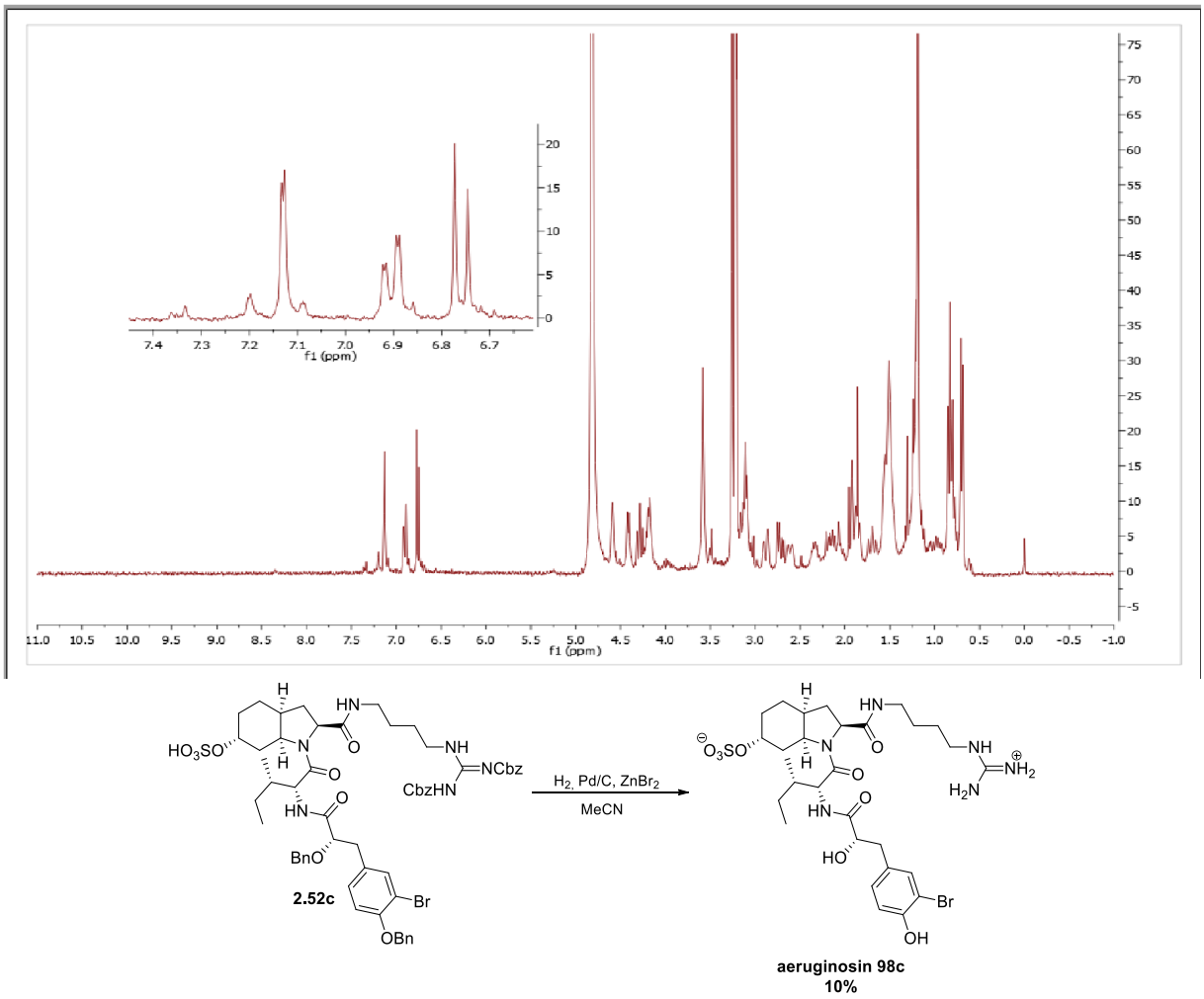


The compound **2.52a** (83 mg, 0.075 mmol) was dissolved in a mixture of AcOEt (2 mL) and MeOH (2 mL) and $Pd(OH)_2/C$ (20 %) (264 mg, 0.38 mmol) was added in one portion. The atmosphere was replaced by hydrogen (1 atm.) by three cycles of vacuum / H_2. After 6 hours, the resulting mixture was filtered through a pad of celite and rinced with EtOAc (50 mL) followed by MeOH (50 mL). The filtrate was concentrated *in vacuo*. Purification by HPLC (Interchim Puriflash 4250, Waters X-Bridge Prep C18, 5µm 19 x 50 mm, H_2O/MeCN : 1/0 to 0/1 during 10 min; RT = 1 min) gave **aeruginosin 98B** (37 mg, 75 %) as a mixture of conformers (84:16). **$[\alpha]_D$**= – 10.3 ° (H_2O, c 0.1) Lit. [72a] **$[\alpha]_D$**= – 5.24 ° (H_2O, c 0.25). **^{1}H NMR (300 MHz, $CDCl_3$)** δ = 9.23 (s, 1H), 8.43 (s, 2H), 8.33 (s, 1H), 7.90 (t, *J* = 5.3 Hz, 1H), 7.60 – 7.41 (m, 3H), 7.35 (d, *J* = 8.5 Hz, 1H), 7.00 (d, *J* = 8.3 Hz, 2H), 6.64 (d, *J* = 8.3 Hz, 2H), 5.87 (s, 1H), 4.47 (dd, *J* = 8.3, 4.6 Hz, 1H), 4.39 – 4.31 (m, 1H), 4.17 (t, *J* = 8.9 Hz, 1H), 4.09 – 4.03 (m, 1H), 4.04 – 3.98 (m, 1H), 3.11 – 3.03 (m, 3H), 3.02 – 2.95 (m, 1H), 2.88 (dd, *J* = 14.2, 3.2 Hz, 1H), 2.63 (dd, *J* = 14.0, 7.4 Hz, 1H), 2.32 – 2.18 (m, 2H), 2.06 – 1.93 (m, 2H), 1.86 (d, *J* = 13.1 Hz, 1H), 1.82 – 1.72 (m, 1H), 1.72 – 1.64 (m, 1H), 1.58 – 1.51 (m, 1H), 1.49 – 1.38 (m, 5H), 1.37 – 1.29 (m, 1H), 1.23 – 1.14 (m, 1H), 1.03 – 0.92 (m, 1H), 0.85 (t, *J* = 7.3 Hz, 3H), 0.67 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.8, 171.5, 168.9, 157.3, 155.7, 130.5, 128.1, 114.7, 72.2, 71.0, 59.9, 54.0, 52.5, 40.3, 39.2, 38.0, 37.7, 35.9, 31.7, 30.7, 26.2, 25.8, 23.4, 19.4, 13.8, 11.8. **HRMS (ESI):** calculated for $C_{29}H_{47}N_6O_9S$ 655.3120 found 655.3115.

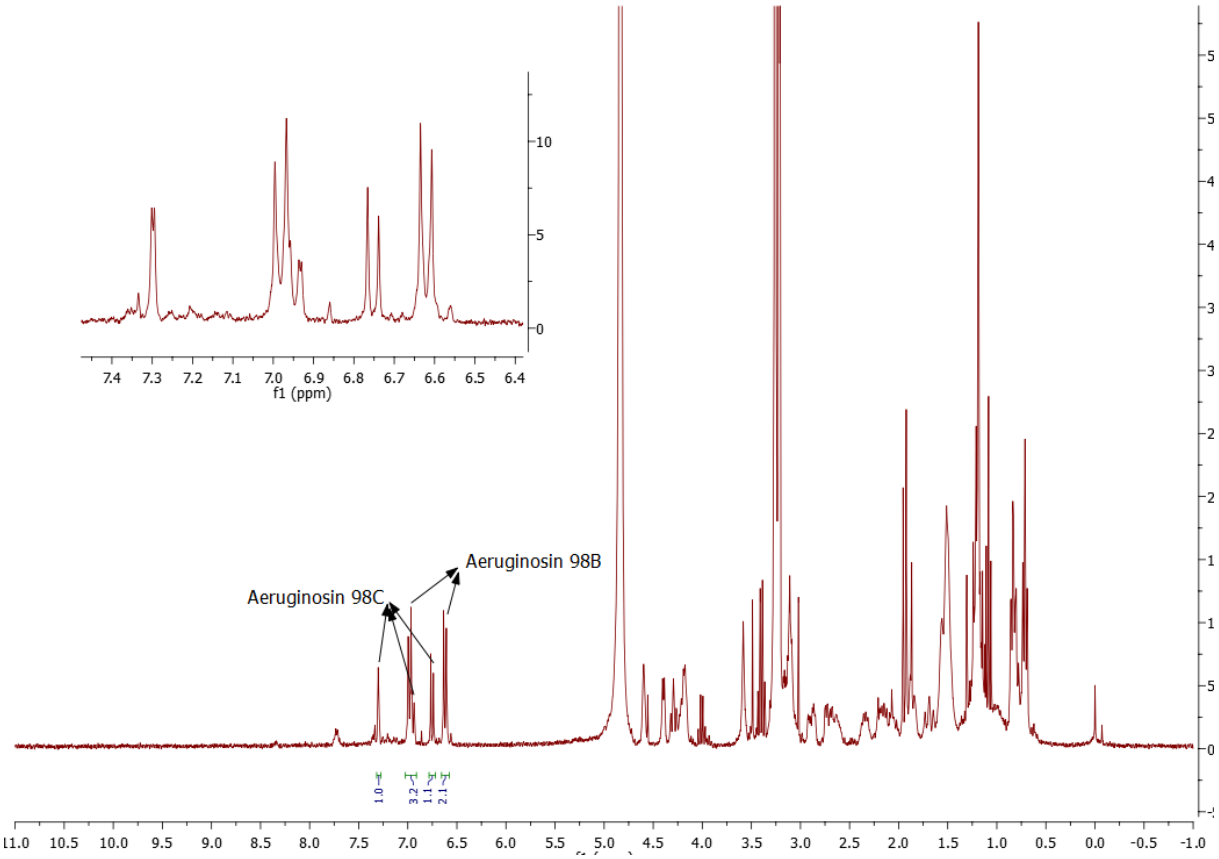


The compound **2.52b** (33.8 mg, 30 µmol) was dissolved in acetonitrile (2 mL) and Pd/C (10 %) (158 mg, 0.15 mmol) and $ZnBr_2$ (33.5 mg, 0.15 mmol) were added in one portion. The atmosphere was replaced by hydrogen (1 atm.) by three cycle of vacuum / H_2. After 6 hours, silica gel was added and the resulting mixture was filtered through a pad of celite and rinced with MeOH (50 mL). The filtrate was concentrated *in vacuo*. The ^{1}H NMR analysis in MeOH-d_4 of the crude mixture showed a total conversion (See spectrum below). Purification by column chromatography (C18, H_2O / MeCN / 1% TFA, 9/1 to 1/1) gave **aeruginosin 98A** (10 mg, 50 %) as a mixture of conformers (80:20) **^{1}H NMR (500 MHz, DMSO-d_6)** δ = 9.94 – 9.84 (m, 1H), 8.37 – 8.21 (m, 1H), 7.84 (br s, 1H), 7.63 (br s, 1H), 7.34 (d, J = 8.5 Hz, 1H), 7.17 (br s, 1H), 6.96 (d, J = 8.0 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 5.88 (br s, 1H), 4.46 (dd, J = 8.3, 4.0 Hz, 1H), 4.38 – 4.32 (m, 1H), 4.16 (t, J = 8.9 Hz, 1H), 4.09 (br s, 1H), 4.06 – 3.97 (m, 1H), 3.18 – 3.03 (m, 3H), 3.03 – 2.95 (m, 1H), 2.89 – 2.82 (m, 1H), 2.70 – 2.62 (m, 1H), 2.32 – 2.18 (m, 2H), 2.04 – 1.92 (m, 2H), 1.91 – 1.81 (m, 1H), 1.81 – 1.71 (m, 1H), 1.73 – 1.64 (m, 1H), 1.56 – 1.49 (m, 1H), 1.49 – 1.34 (m, 5H), 1.36 – 1.24 (m, 3H), 1.19 – 1.11 (m, 2H), 0.97 – 0.88 (m, 1H), 0.84 (t, J = 7.1 Hz, 3H), 0.64 (d, J = 6.6 Hz, 3H). .**^{13}C NMR (126 MHz, DMSO-d_6)** δ = 172.5, 171.7, 169.1, 156.7, 151.5, 130.8, 129.7, 129.4, 119.0, 116.2, 71.8, 71.7, 59.9, 54.1, 52.6, 40.4, 38.8, 38.0, 37.6, 36.0, 31.7, 30.8, 26.3, 26.0, 25.9, 23.5, 19.4, 13.8, 11.9. **HRMS (ESI):** calculated for $C_{29}H_{46}ClN_6O_9S$ 689.2736 found 689.2718.



The compound **44c** (36.2 mg, 31 µmol) was dissolved in acetonitrile (2 mL) and Pd/C (10 %) (163 mg, 0.15 mmol) and $ZnBr_2$ (35 mg, 0.15 mmol) were added in one portion. The atmosphere was replaced by hydrogen (1 atm.) by three cycle of vacuum / H_2. After 6 hours, silica gel was added and the resulting mixture was filtered through a pad of celite and rinced with MeOH (50 mL). The filtrate was concentrated *in vacuo*. The ^{1}H NMR analysis in MeOH-d_4 of the crude mixture showed a total conversion of 1:1 mixture of aeruginosin 98B and 98C. (See spectrum below). The mixture was purified by HPLC (Waters , Sunfire Waters Prep C18, 5 µm 19 x 150 mm, H_2O/MeCN 0.1% Formic acid; isocratic 8:2; 20 mL/min; RT = 8.72 min) and **aeruginosin 98C**[72f] (**1d**) (2 mg) was obtained as a mixture of conformers (82:18) with unexpected 9 % yield due to loss of material during the purification.

^{1}H NMR (500 MHz, DMSO-d_6) δ = 10.01 (br s, 1H), 8.40 (br s, 1H), 7.95 (br s, 1H), 7.89 – 7.78 (m, 1H), 7.44 (d, J = 8.9 Hz, 1H), 7.35 (s, 1H), 7.33 (d, J = 1.7 Hz, 1H), 7.29 (d, J = 1.8 Hz, 2H), 7.00 (dd, J = 8.2, 1.7 Hz, 1H), 6.83 (d, J = 8.2 Hz, 1H), 5.89 (br s, 1H), 4.49 – 4.42 (m, 1H), 4.36 (br s, 1H), 4.16 (t, J = 8.9 Hz, 1H), 4.08 (br s, 1H), 4.06 – 3.98 (m, 1H), 3.15 – 2.95 (m, 4H), 2.86 (dd, J = 14.0, 3.1 Hz, 1H), 2.67 (dd, J = 14.0, 7.1 Hz, 1H), 2.36 – 2.17 (m, 2H), 2.06 – 1.92 (m, 2H), 1.91 – 1.82 (m, 1H), 1.82 – 1.72 (m, 1H), 1.72 – 1.63 (m, 1H), 1.57 – 1.50 (m, 1H), 1.51 – 1.35 (m, 5H), 1.37 – 1.29 (m, 1H), 1.19 – 1.10 (m, 1H), 0.99 – 0.90 (m, 1H), 0.85 (t, J = 7.2 Hz, 3H), 0.65 (d, J = 6.5 Hz, 3H).**^{13}C NMR (126 MHz, DMSO-d_6)** δ = 172.3, 171.5, 169.0, 156.9, 152.4, 133.6, 130.0, 130.0, 115.8, 108.6, 71.7, 70.8, 59.9, 54.0, 52.5, 40.4, 38.8, 37.9, 37.5, 35.9, 31.7, 30.7, 26.2, 25.8, 23.4, 19.4, 13.8, 11.9. **HRMS (ESI):** calculated for $C_{29}H_{46}BrN_6O_9S$ 733.2230 found 733.2204.



3. Synthesis of Strained γ-Lactams by Palladium(0)-Catalyzed C(sp^3)–H Alkenylation and Application to Alkaloid Synthesis

3.1. General procedures

General procedure A: General procedure for the C(sp^3)-H activation

In the glovebox, palladium allyl chloride (5 mol%.), PPh_3 (20 mol%), cesium carbonate (1.5 equiv) and pivalic acid (30 mol%) were added to a reaction tube containing a magnetic stir bar. The protected amide (1 equiv) was added to second, dried reaction tube, which was evacuated and backfilled with argon three times. Then, mesitylene (1 mL) was added and the solution was transferred to the first tube containing the catalyst under argon. The reaction was placed in a pre-heated oil batch or metal block and stirred overnight (12 h) at 160°C. The mixture was diluted with ethyl acetate, filtered over Celite and concentrated under reduced pressure. The crude product was purified by preparative thin layer chromatography or by flash chromatography.

General procedure B: Amide formation

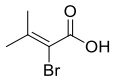
A carboxylic acid (1 equiv) was dissolved under exclusion of moisture in DCM. Oxalyl chloride (1.3 equiv) and a catalytic quantity of DMF were added. The mixture was stirred for 1h at room temperature and disappearance of the starting material was checked by GCMS. Then, the amine (2-6 equiv) and a solution of NaOH (1M, 8 equiv) were added at 0°C. The reaction mixture was allowed to warm up to room temperature and was stirred vigorously overnight. After quenching with brine, the aq. phase was extracted three times with DCM. The unified organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography.

General procedure C: Amide protection

To a stirred solution of amide (1 equiv), in THF under argon atmosphere, a solution of NaHMDS (2 equiv) in THF was added dropwise at 0°C. The mixture was stirred for 30 minutes and allowed to warm up to room temperature. Then, the electrophile (2 equiv) was added dropwise. The reaction was stirred for at least two hours, then quenched with a sat. solution of $NaHCO_3$ and extracted with ethyl acetate. The organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography.

3.2. Synthesis of bromoalkenes

2-Bromo-3-methylbut-2-enoic acid 3.17[183]



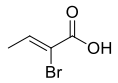
Chemical Formula: $C_5H_7BrO_2$
Exact Mass: 177,9629

Small scale synthesis : To a stirred solution of 3-methylbut-2-enoic acid (200 mg, 2.00 mmol, 1.0 equiv) in DCM (2 mL), was added bromine (351 mg, 2.20 mmol, 1.1 equiv) dropwise at 0°C. The mixture was stirred 12 hours. Then quenched with saturated solution of $Na_2S_2O_3$ to remove excess of bromine and extracted three times with DCM. The organic layer was dried over $MgSO_4$ and concentrated to give the dibrominated acid. The product was dissolved in THF and piperidine (967 µL, 9.80 mmol, 4.9 equiv) was added in one portion at 0°C. The solution was stirred for 24 h at room temperature and then quenched with aq. HCl (5 M). The product was extracted with ethyl acetate. The collected organic layers were dried over $MgSO_4$ and concentrated to give the 2-bromo-3-methylbut-2-enoic acid **3.17** as a yellow powder (319 mg, 1.78 mmol, 89% yield).

Gram scale synthesis : To a stirred solution of 3-methylbut-2-enoic acid (10 g, 99.9 mmol, 1.0 equiv) in DCM (70 mL), was added bromine (5.64 mL, 109.9 mmol, 1.1 equiv) dropwise at 0°C. The mixture was stirred 12 hours. Then quenched with saturated solution of $Na_2S_2O_3$ to remove excess of bromine and extracted three times with DCM. The organic layer was dried over $MgSO_4$ and concentrated to give the dibrominated acid. The product was dissolved in THF (100 mL) and piperidine (48 mL, 490 mmol, 4.9 equiv) was added in one portion at 0°C. The solution was stirred for 24 h at room temperature and then HCl gas was bubbled in the organic phase during 2 hours. The crude product was filtrated on a pad of celite and concentrated to give the 2-bromo-3-methylbut-2-enoic acid **3.17** as a brown oil (10 g, 55.86 mmol, 56% yield).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 10.7 (s, 1 H), 2.20 (s, 3 H), 2.10 (s, 3 H). **^{13}C NMR ($CDCl_3$, 75 MHz):** δ = 169.4, 153.7, 108.7, 28.5, 23.8. **MS (EI, 70 eV, 200 °C):** m/z (%) = 178.1 [M]$^{+\cdot}$ **IR (neat):** ν = 1620 cm^{-1} **Melting point:** 73-75 °C

(*Z*)-2-Bromobut-2-enoic acid

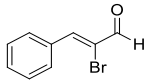


Chemical Formula: $C_4H_5BrO_2$
Exact Mass: 163,9473

Methyl (2*Z*)-2-bromobut-2-enoate was prepared as described previously[184].
Methyl (2*Z*)-2-bromobut-2-enoate (1.4 g, 7.82 mmol, 1 equiv) was dissolved in THF (7 ml) and a solution of LiOH (562 mg, 23.46 mmol, 3 equiv) in water (8 ml) was added. The solution was stirred at overnight at room temperature. The solution was acidified with an aq. solution of HCl (1 N) until pH < 3 and then three times extracted with DCM. The unified org. phase was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure affording 750 mg (4.55 mmol, 58%) of a white solid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 11.38 (br. s., 1 H), 7.55 (q, *J*=6.8 Hz, 1 H), 1.99 (d, *J*=7.0 Hz, 3 H). **^{13}C[136] NMR ($CDCl_3$, 101 MHz):** δ = 168.1, 144.9, 116.7, 18.3. **LRMS (ESI)** calcd for $C_4H_9BrO_2$ ($[M-H]^-$): 162.9; found: 162.9; **IR(neat):** ν = 2821, 2645, 2522, 1673, 1615, 1283 cm^{-1}. **Mp** = 106-108 °C. **HRMS(ESI):** calcd for $C_4H_6BrO_2$ ($[M+H]^+$): 164.9546; found: 164.9544;

(Z)-2-bromo-3-phenylacrylaldehyde

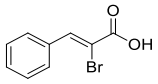


Chemical Formula: C_9H_7BrO
Exact Mass: 209,9680

To a stirred solution of cinnamaldehyde (8.0 g, 60.5 mmol, 1.0 equiv) in DCM (64 mL), was added bromine (11.6 g, 72.6 mmol, 1.2 equiv) dropwise at 0°C. The mixture was stirred 30 min. Then triethylamine (18.4 g, 181.6 mmol, 3.0 equiv) was added and the reaction was stirred for 1 hour. Quenched with saturated solution of $Na_2S_2O_3$ to remove excess of bromine and extracted three times with DCM. The organic layer was dried over $MgSO_4$ and concentrated to give (*Z*)-2-bromo-3-phenylacrylaldehyde as a white powder (8.4 g, 39.8 mmol, 66% yield). Spectroscopic data are consistent with those previously reported.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.40 - 7.54 (m, 3 H), 7.91 (s, 1 H), 7.96 - 8.07 (m, 2 H), 9.36 (d, *J*=0.4 Hz, 1 H) ppm. **MS (EI, 70 eV, 200 °C):** 209.9 $[M]^{+\cdot}$

(*Z*)-2-bromo-3-phenylacrylic acid

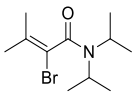


Chemical Formula: $C_9H_7BrO_2$
Exact Mass: 225,9629

A solution of $NaClO_2$ (4.8 g, 53.1 mmol, 1.4 equiv) in water was added dropwise to a stirred solution of (*Z*)-2-bromo-3-phenyl-propenal (8.0 g, 37.9 mmol, 1.0 equiv), an aq. solution of NaH_2PO_4 (1.1 g, 15 mL, 9.5 mmol, 0.25 equiv) and an aq. solution of H_2O_2 (30%, 3.55 mL, 45.5 mmol, 1.2 equiv) in MeCN (38 mL), at 0°C. The mixture was stirred 2 hours and then quenched with Na_2CO_3 in water until pH=10 was reached. The reaction mixture was extracted with Et_2O (3x 60 mL) and the aq. phase was acidified with aq. HCl (1M), until the pH=1 was reached. The precipitate formed was filtered and washed with cold water. The white powder was collected and dried overnight to give the (*Z*)-2-bromo-3-phenylacrylic acid (7.1 g, 31.3 mmol, 59 %). Spectroscopic data are consistent with those previously reported.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.39 - 7.52 (m, 3 H), 7.84 - 7.97 (m, 2 H), 8.37 (s, 1 H) ppm. **MS (EI, 70 eV, 200 °C):** 226.1 $[M]^{+\cdot}$

2-Bromo-*N*,*N*-diisopropyl-3-methylbut-2-enamide 3.13a

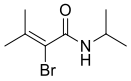


Chemical Formula: $C_{11}H_{20}BrNO$
Exact Mass: 261,0728

Following general procedure **B**, 2-bromo-3-methylbut-2-enoic acid **3.17** (200 mg, 1.12 mmol, 1.0 equiv) was reacted with oxalyl chloride (124 µL, 1.45 mmol, 1.3 equiv), DMF (2 drops), diisopropylamine (947 µL, 6.70 mmol, 6.0 equiv) and aq. NaOH (1 M, 8.9 mL, 8.90 mmol, 8.0 equiv) in DCM (8.9 mL) for 12 hours. The crude product was purified by flash chromatography (eluent: CyHex/EtOAc/Et_3N 90:10:2) affording 2-Bromo-*N*,*N*-diisopropyl-3-methylbut-2-enamide **3.13a** (234 mg, 0.89 mmol, 80%) as a white solid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.00 (sep., J=6.7 Hz, 1 H), 3.38 (sep., J=6.7 Hz, 1 H), 1.87 (s, 3 H), 1.81 (s, 3 H), 1.41 (d, J=6.7 Hz, 3 H), 1.44 (d, J=6.7 Hz, 3 H), 1.18 (d, J=6.7 Hz, 3 H), 1.13 (d, J=6.7 Hz, 3 H). **$^{13}C^{136}$ NMR ($CDCl_3$, 75 MHz):** δ = 165.6, 133.2, 110.1, 51.2, 45.7, 22.8, 21.4, 21.0, 20.4, 20.3, 19.7. **IR (neat):** ν = 2971, 1620 cm^{-1}. **MS (EI, 70 eV, 200 °C):** m/z (%) = 260.9 $[M]^{+\cdot}$. **Melting point:** 71-73 °C

2-Bromo-*N*-isopropyl-3-methylbut-2-enamide 3.19

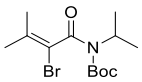


Chemical Formula: $C_8H_{14}BrNO$
Exact Mass: 219,0259

Following general procedure **B**, 2-bromo-3-methylbut-2-enoic acid **3.17** (319 mg, 1.78 mmol, 1.0 equiv), oxalyl chloride (199 µL, 2.32 mmol, 1.3 equiv), DMF (2 drops), isopropylamine (1.5 mL, 10.69 mmol, 6.0 equiv) and aq. NaOH (1 M) (14.3 mL, 14.26 mmol, 8.0 equiv) in DCM (14,5 mL) were allowed to react for 12 hours. The obtained oil was purified by flash chromatography (eluent: CyHex/EtOAc/Et_3N 90:10:2). The 2-bromo-*N*-isopropyl-3-methylbut-2-enamide **3.19** was obtained as a white solid (350 mg, 1.59 mmol, 89%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.94 (s, 1 H), 4.06 (sept, J=6.6 Hz, 1 H), 2.07 (s, 3 H), 1.95 (s, 3 H), 1.18 (d, J=6.6 Hz, 6 H). **^{13}C^{136} NMR ($CDCl_3$, 75 MHz):** δ = 164.0, 142.6, 111.3, 42.1, 26.3, 22.7, 22.6 (2C). **IR (neat):** ν = 3251, 2971, 1627, 697 cm^{-1}. **MS (EI, 70 eV, 200 °C):** m/z (%) = 219.1 $[M]^{+\cdot}$. **Melting point:** 64-66 °C

***Tert*-butyl (2-bromo-3-methylbut-2-enoyl)(isopropyl)carbamate 3.13b**

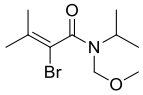


Chemical Formula: $C_{13}H_{22}BrNO_3$
Exact Mass: 319,0783

To a solution of 2-bromo-3-methyl-*N*-(propan-2-yl)but-2-enamide **3.19** (200 mg, 0.91 mmol, 1 equiv) in acetonitrile (2 mL) was added Boc_2O (218 mg, 0.21 mL, 1.00 mmol, 1.1 equiv). The solution was warmed to 70°C then DMAP (16 mg, 0.13 mmol, 14 mol%) was added. The reaction was monitored by TLC every 30 min and portions of Boc_2O (0.5 equiv) and DMAP (5 mol%) were added until after 3h the conversion was complete. The reaction was quenched with a sat. aq. $NaHCO_3$, extracted with DCM and dried over $MgSO_4$. The crude product was purified by flash chromatography (eluent: Cyclohex/EtOAC/Et_3N 96:4:2) affording Tert-butyl (2-bromo-3-methylbut-2-enoyl)(isopropyl)carbamate **3.13b** (260 mg 0.81 mmol, 89 %) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.64 (sep, J=6.9 Hz, 1 H), 1.86 (s, 3 H), 1.82 (s, 3 H), 1.43 (s, 9 H), 1.29 (d, J=6.9 Hz, 6 H). **^{13}C ^{136} NMR ($CDCl_3$, 75 MHz):** δ = 167.5, 152.3, 137.0, 111.7, 83.3, 48.1, 27.9 (3 C), 24.2, 21.8 (2 C), 20.0. **IR (neat):** ν = 2976, 2935, 1734, 1667 cm^{-1}. **MS (EI, 70 eV, 200 °C):** m/z (%) = 262.0 $[M - C_4H_9]^{+\cdot}$

2-Bromo-*N*-(ethoxymethyl)-*N*-isopropyl-3-methylbut-2-enamide 3.13c

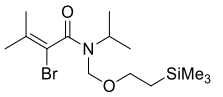


Chemical Formula: $C_{10}H_{18}BrNO_2$
Exact Mass: 263,0521

Following general procedure **C**, 2-bromo-*N*-isopropyl-3-methylbut-2-enamide **3.19** (200 mg, 0.91 mmol, 1.0 equiv) was reacted with NaHMDS (364 µL, 1.82 mmol, 2 equiv), ethoxymethyl chloride (170 µL, 1.82 mmol, 2.0 equiv) in THF (4 mL). The obtained oil was purified by flash chromatography (eluent: CyHex/EtOAc/Et_3N 90:10:2) affording 2-bromo-*N*-(ethoxymethyl)-*N*-isopropyl-3-methylbut-2-enamide **3.13c** as a colorless oil (215 mg, 0.77 mmol, 85%).

^{1}H NMR ($CDCl_3$, 300 MHz, mixture of two conformers, ratio = 0.55/0.45): δ= 4.64, 4.90 (2 m, J=3 Hz, together 2 H), 4.08, 4.46 (2 sep., J=6.7 Hz, together 1 H), 3.36, 3.57 (2 q, J=7 Hz, together 2 H), 1.77-1.86 (d, J=9.0 Hz, d, J=5.9 Hz, together 6 H), 1.22 (s, 3 H), 1.20 (s, 3 H), 1.13 (m, 3 H). **^{13}C {^{1}H} NMR ($CDCl_3$, 75 MHz):** δ = 168.0-167.2, 136.1-134.9, 108.23-108.17, 76.1-70.2, 64.4-63.2, 50.1-46.1, 23.1-23.0, 21.9-21.8, 22.3-21.4, 15.3, 15.0. **IR (neat):** ν = 2957, 2933, 1644, 1076 cm^{-1}. **MS (EI, 70 eV, 200 °C):** m/z (%) = 277.0 $[M]^{+\cdot}$

2-Bromo-*N*-isopropyl-3-methyl-N-((2-(trimethylsilyl)ethoxy)methyl)but-2-enamide 3.13e

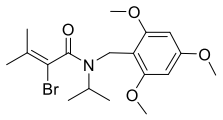


Chemical Formula: $C_{14}H_{28}BrNO_2Si$
Exact Mass: 349,1073

Following general procedure **C**, 2-bromo-*N*-isopropyl-3-methylbut-2-enamide **3.19** (200 mg, 0.909 mmol, 1.0 equiv) was reacted with NaHMDS (364 µL, 1.817 mmol, 2 equiv), 2-(trimethylsilyl)ethoxymethyl chloride (322 µL, 1.817 mmol, 2.0 equiv) in THF (4 mL). The crude product was purified by flash chromatography (eluent: CyHex/EtOAc/Et_3N 90:10:2) affording 2-Bromo-*N*-isopropyl-3-methyl-*N*-((2-(trimethylsilyl)ethoxy)methyl)but-2-enamide **3.13e** as a colorless oil (285 mg, 0.813 mmol, 90% yield).

^{1}H NMR ($CDCl_3$, 300 MHz, mixture of two conformers, ratio = 0.57/0.43): δ = 5.03 – 4.81 (m, 1H), 4.66 (d, J = 9.7 Hz, 1H), 4.56 – 4.02 (m, 1H), 3.70 – 3.55 (m, 1H), 3.67-3.40 (m, 1H), 1.90 (d, J = 5.0 Hz, 3H), 1.81 (d, J = 9.7 Hz, 3H), 1.25 (d, J = 8.3 Hz, 6H), 0.99 – 0.77 (m, 2H), 0.00 (d, J = 3.3 Hz, 9H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** δ = 167.8, 135.3, 108.2, 77.2, 69.7, 65.9-65.2, 49.9-46.1, 22.9, 21.7, 20.3, 18.1, 0 (3 C). **IR (neat):** ν = 2890, 1645, 1044 cm^{-1}. **MS (EI, 70 eV, 200 °C):** m/z (%) = 349.1 $[M]^{+\cdot}$

2-Bromo-*N*-isopropyl-3-methyl-*N*-(2,4,6-trimethoxybenzyl)but-2-enamide 3.13f

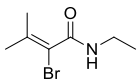


Chemical Formula: $C_{18}H_{26}BrNO_4$
Exact Mass: 399,1045

Following general procedure **B**, 2-bromo-3-methylbut-2-enoic acid **3.17** (524 mg, 2.93 mmol, 1.0 equiv) was reacted with oxalyl chloride (327 µL, 3.81 mmol, 1.3 equiv), DMF (2 drops), *N*-(2,4,6-trimethoxybenzyl)propan-2-amine (2.1 g, 8.79 mmol, 3.0 equiv) and aq. NaOH (1 M, 23.4 mL, 23.4 mmol, 8.0 equiv) in DCM (15 mL) for 12 hours. The crude product was purified by flash chromatography (eluent: CyHex/EtOAc 90:10) affording 2-Bromo-*N*-isopropyl-3-methyl-*N*-(2,4,6-trimethoxybenzyl)but-2-enamide **3.13f** (973 mg ,2.43 mmol, 83%) as a yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz, mixture of two conformers, ratio = 0.50/0.50): δ= 6.12 – 6.05 (m, 2H), 4.93 – 4.64 (m, 1H), 4.56 – 4.38 (m, 1H), 4.18 – 4.06 (m, 0.5H), 3.84 – 3.76 (m, 9H), 3.77 – 3.70 (m, 0.5H), 1.90 – 1.87 (m, 3H), 1.87 – 1.83 (m, 3H), 1.18 – 1.10 (m, 3H), 1.08 – 0.93 (m, 3H). **^{13}C {^{1}H} NMR ($CDCl_3$, 75 MHz):** δ = 166.8, 166.1, 161.3, 160.9, 160.0, 159.7, 134.9, 133.5, 111.7, 110.0, 107.6, 104.8, 90.4, 90.3, 55.7, 55.5, 55.4, 55.4, 51.0, 48.9, 41.0, 32.1, 23.6, 23.1, 21.7, 21.4, 21.3, 20.5, 19.6, 19.1. **IR (neat):** ν = 2937, 1630, 1606, 1418, 1204 cm^{-1}. **HRMS(ESI):** calcd for $C_{18}H_{27}BrNO_4$ ($[M+H]^+$): 400.1118; found: 400.1125;

2-Bromo-*N*-ethyl-3-methylbut-2-enamide 3.19g



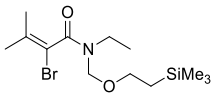
Chemical Formula: $C_7H_{12}BrNO$
Exact Mass: 205,0102

Following general procedure **B**, 2-bromo-3-methylbut-2-enoic acid **3.17** (500 mg, 2.79 mmol, 1 equiv) was reacted with oxalyl chloride (311 µL, 3.63 mmol, 1.3 equiv), DMF (2 drops), ethylamine (1.03 mL, 16.76 mmol, 6.0 equiv) and aq. NaOH (1M, 22 mL, 22.00 mmol, 8.0 equiv) in DCM (22 mL). The crude product was purified by flash chromatography (eluent: CyHex/EtOAc/Et_3N 90:10:2) affording 2-Bromo-*N*-ethyl-3-methylbut-2-enamide **3.19g** (523 mg, 2.54 mmol, 91%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.23 (s, 1H), 3.61 – 3.09 (m, 2H), 2.08 (s, 3H), 2.04 (s, 3H), 1.45 – 1.10 (t, J=10.2 Hz, 3H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** δ = 164.7, 142.9, 111.0, 35.0,

26.3, 22.8, 14.7. **IR (neat):** ν = 3269, 1519,1296 cm^{-1}. **MS (EI, 70 eV, 200 °C):** m/z (%) = 206.2 $[M]^{+\cdot}$

2-Bromo-*N*-ethyl-3-methyl-*N*-((2-(trimethylsilyl)ethoxy)methyl)but-2-enamide 3.13g

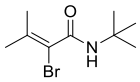


Chemical Formula: $C_{13}H_{26}BrNO_2Si$
Exact Mass: 335,0916

Following general procedure **C**, 2-bromo-*N*-ethyl-3-methylbut-2-enamide **3.19g** (200 mg, 0.97 mmol, 1.0 equiv) was reacted with NaHMDS (389 µL, 1.94 mmol, 2.0 equiv) and 2 (trimethylsilyl)ethoxymethyl chloride (344 µL, 1.94 mmol, 2.0 equiv) in THF (3 mL). The crude product was purified by flash chromatography (eluent: CyHex/EtOAc/Et_3N 90:10:2) affording 2-Bromo-*N*-ethyl-3-methyl-*N*-((2-(trimethylsilyl)ethoxy)methyl)but-2-enamide **3.13g** (278 mg, 0.83 mmol, 85% yield) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.93 – 4.54 (m, 2H), 3.57 – 3.33 (m, 4H), 1.92 – 1.68 (m, 6H), 1.17 – 1.05 (m, 3H), 0.91 – 0.79 (m, 2H), -0.04 – -0.10 (m, 9H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** δ = 166.4, 136.3, 107.6, 78.4, 65.6, 38.8, 23.1, 21.7, 18.0, 12.4,-1.4. **IR (neat):** ν = 2950, 1646, 1419 cm^{-1}. **HRMS (ESI):** calcd for $C_{13}H_{27}BrNO_2Si$ ($[M+H]^+$) : 336.0989; found: 336.0990;

2-Bromo-*N*-(*tert*-butyl)-3-methylbut-2-enamide 3.19h

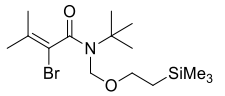


Chemical Formula: $C_9H_{16}BrNO$
Exact Mass: 233,0415

Following general procedure **B**, 2-bromo-3-methylbut-2-enoic acid **3.17** (500 mg, 2.79 mmol, 1.0 equiv) was reacted with oxalyl chloride (311 µL, 3.63 mmol, 1.3 equiv), DMF (2 drops), *tert*-butylamine (1.77 mL, 16.76 mmol, 6.0 equiv) and aq. NaOH (1M, 22 mL, 22 mmol, 8.0 equiv) in DCM (22 mL). The crude product was purified by flash chromatography (eluent: CyHex/EtOAc/Et_3N 90:10:2) affording 2-Bromo-*N*-(tert-butyl)-3-methylbut-2-enamide **3.19h** (582 mg, 2.49 mmol, 89%) as a white solid

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.83 (s, 1H), 2.05 (s, 3H), 1.93 (s, 3H), 1.38 (s, 9H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** δ = 164.4, 140.9, 111.9, 51.8, 28.7, 25.8, 22.5. **IR (neat):** ν = 2971, 1620 cm^{-1}. **MS (EI, 70 eV, 200 °C):** m/z (%) = 233.1 $[M]^{+\cdot}$. **Melting point:** 70-72 °C

2-Bromo-*N*-(*tert*-butyl)-3-methyl-*N*-((2-(trimethylsilyl)ethoxy)methyl)but-2-enamide 3.13h

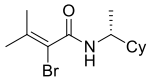


Chemical Formula: $C_{15}H_{30}BrNO_2Si$
Exact Mass: 363,1229

Following general procedure **C**, 2-bromo-*N*-(*tert*-butyl)-3-methylbut-2-enamide **3.17** (200 mg, 0.85 mmol, 1.0 equiv) was reacted with NaHMDS (342 µL, 1.72 mmol, 2.0 equiv) and 2 (trimethylsilyl)ethoxymethyl chloride (303 µL, 1.718 mmol, 2.0 equiv) in THF (3 mL). After the addition of SEM chloride the reaction was heated at 60°C overnight. The crude product was purified by flash chromatography (eluent: CyHex/EtOAc/Et_3N 90:10:2) affording 2-Bromo-*N*-(tert-butyl)-3-methyl-*N*-((2-(trimethylsilyl)ethoxy)methyl)but-2-enamide **3.13h** (274 mg, 0.75 mmol, 88% yield) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.70 (m, 2H), 3.50 (m, 2H), 1.87 (s, 3H), 1.81 (s, 3H), 1.46 (s, 9H), 0.87 (m, 2H), 0.00 (s, 9H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** δ = 169.4, 136.5, 111.6, 61.1, 78.0, 58.6, 29.5 (3 C), 24.7, 23.2, 19.5, 0.0 (3 C). **IR (neat):** ν = 2987, 1663 cm^{-1}. **MS (EI, 70 eV, 200 °C):** m/z (%) = 362.2 $[M]^{+\cdot}$

(*R*)-2-Bromo-*N*-(1-cyclohexylethyl)-3-methylbut-2-enamide 3.19i

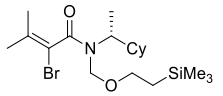


Chemical Formula: $C_{13}H_{22}BrNO$
Exact Mass: 287,0885

Following general procedure **B**, 2-bromo-3-methylbut-2-enoic acid **3.17** (500 mg, 2.79 mmol, 1.0 equiv) was reacted with oxalyl chloride (311 µL, 3.63 mmol, 1.3 equiv), DMF (2 drops), (*R*)-1-cyclohexylethanamine (2.49 mL, 16.76 mmol, 6.0 equiv) and aq. NaOH (1M, 22 mL, 22.00 mmol, 8.0 equiv) in DCM (22 mL). The crude product was purified by flash chromatography (eluent: CyHex/EtOAc/Et_3N 90:10:2) affording (*R*)-2-Bromo-*N*-(1-cyclohexylethyl)-3-methylbut-2-enamide **3.19i** (531 mg, 1.84 mmol, 66%) as a white solid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.94 (s, 1H), 3.89 (m, 1H), 2.12 (s, 3H), 1.99 (s, 3H), 1.68 (d, J = 10.7 Hz, 3H), 1.31 – 1.10 (m, 11H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** 164.9, 141.2, 111.2, 50.0, 43.1, 29.1, 29.0, 26.3, 26.2 (2 C), 22.7, 18.1, 17.8. **IR (neat):** ν = 3277, 2980, 2950, 1629 cm^{-1}. **MS (EI, 70 eV, 200 °C):** m/z (%) = 287.0 $[M]^{+\cdot}$ **Melting point:** 79-81 °C. **Optical rotation:** $[\alpha]_D^{20}$ = +2.7 (c = 1.01, $CHCl_3$)

(*R*)-2-Bromo-*N*-(1-cyclohexylethyl)-3-methyl-*N*-((2-(trimethylsilyl)ethoxy)methyl)but-2-enamide 3.13i

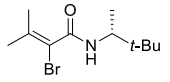


Chemical Formula: $C_{19}H_{36}BrNO_2Si$
Exact Mass: 417,1699

Following general procedure **C**, (*R*)-2-bromo-*N*-(1-cyclohexylethyl)-3-methylbut-2-enamide **3.19i**(200 mg, 0.69 mmol, 1.0 equiv) was reacted with NaHMDS (278 µL, 1.39 mmol, 2.0 equiv), 2 (trimethylsilyl)ethoxymethyl chloride (246 µL, 1.39 mmol, 2.0 equiv) in THF (2 mL). The crude product was purified by flash chromatography (eluent: CyHex/EtOAc/Et_3N 90:10:2) affording (*R*)-2-Bromo-*N*-(1-cyclohexylethyl)-3-methyl-*N*-((2-(trimethylsilyl)ethoxy)methyl)but-2-enamide **3.13i** (267 mg, 0.64 mmol, 92%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.18 – 4.36 (m, 2H), 3.99 (m, 1H), 3.70 – 3.44 (m, 1H), 3.40 (t, J = 7.8 Hz, 1H), 1.90 (s, 3H), 1.82 (s, 3H), 1.74 (d, J = 13.9 Hz, 3H), 1.64 (m, 2H), 1.22 (m, 4H), 0.88 (m, 6H), -0.00 (s, 9H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** complex mixture of rotamers **IR (neat):** ν = 2921, 1645 cm^{-1}. **Optical rotation:** $[\alpha]_D^{20}$ = -11.6 (c = 0.97, $CHCl_3$) **MS (EI, 70 eV, 200 °C):** m/z (%) = 417.0 $[M]^{+\cdot}$

***(R)*-2-Bromo-*N*-(3,3-dimethylbutan-2-yl)-3-methylbut-2-enamide 3.19j**

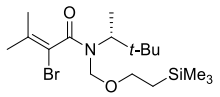


Chemical Formula: $C_{11}H_{20}BrNO$
Exact Mass: 261,0728

Following general procedure **B**, 2-bromo-3-methylbut-2-enoic acid **3.17** (500 mg, 2.79 mmol, 1.0 equiv) was reacted with oxalyl chloride (311 µL, 3.63 mmol, 1.3 equiv), DMF (2 drops), (*R*)-3,3-dimethylbutan-2-amine (1.14 mL, 8.38 mmol, 3.0 equiv) and aq. NaOH (1M, 22 mL, 22.00 mmol, 8.0 equiv) in DCM (22 mL). The crude product was purified by flash chromatography (eluent: CyHex/EtOAc/Et_3N 90:10:2) affording (*R*)-2-Bromo-*N*-(3,3-dimethylbutan-2-yl)-3-methylbut-2-enamide **3.19j** (451 mg, 2.07 mmol, 74%) as a white solid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.05 (d, J = 9.2 Hz, 1H), 3.70 (q, J = 6.8 Hz, 1H), 1.89 (s, 3H), 1.78 (s, 3H), 0.92 (d, J = 6.9 Hz, 3H), 0.76 (s, 9H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** δ = 163.9, 141.2, 111.2, 53.1, 34.3, 26.0 (3 C), 25.6, 22.4, 15.7. **IR (neat):** ν = 3271, 2967, 1631 cm^{-1}. **Optical rotation:** $[\alpha]_D^{20}$ = -31.5 (c = 0.93, $CHCl_3$). **MS (EI, 70 eV, 200 °C):** m/z (%) = 261.3 $[M]^{+\cdot}$. **Melting point:** 83-85 °C

(*R*)-2-Bromo-*N*-(3,3-dimethylbutan-2-yl)-3-methyl-*N*-((trimethylsilyl)ethoxy)methyl)but-2-enamide 3.13j

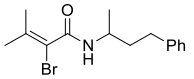


Chemical Formula: $C_{17}H_{34}BrNO_2Si$
Exact Mass: 391,1542

Following general procedure **C**, (*R*)-2-bromo-*N*-(3,3-dimethylbutan-2-yl)-3-methylbut-2-enamide **3.19j** (200 mg, 0.76 mmol, 1.0 equiv) was reacted with NaHMDS (305 µL, 1.53 mmol, 2.0 equiv), 2 (trimethylsilyl)ethoxymethyl chloride (271 µL, 1.53 mmol, 2.0 equiv) in THF (3 mL). The crude product was purified by flash chromatography (eluent: CyHex/EtOAc/Et_3N 90:10:2) affording (*R*)-2-Bromo-*N*-(3,3-dimethylbutan-2-yl)-3-methyl-*N*((trimethylsilyl)ethoxy) methyl)but-2-enamide 3.13j (240 mg, 0.61 mmol, 80%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.86 – 4.25 (m, 2H), 3.86 – 3.25 (m, 2H), 3.32 (s, 1H), 1.90 (s, 3H), 1.82 (s, 3H), 1.32 – 1.06 (m, 3H), 0.93 (s, 9H), 0.85 (m, 2H), -0.00 (s, 9H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** complex mixture of rotamers. **IR (neat):** ν = 2952, 1642 cm^{-1}. **Optical rotation:** $[\alpha]_D^{20}$ = -29.3 (c = 0.98, $CHCl_3$). **MS (EI, 70 eV, 200 °C):** m/z (%) = 392.4 $[M]^{+\cdot}$

2-Bromo-3-methyl-*N*-(4-phenylbutan-2-yl)but-2-enamide 3.19k



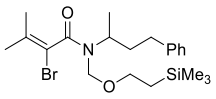
Chemical Formula: $C_{15}H_{20}BrNO$
Exact Mass: 309,0728

Following general procedure **B**, 2-bromo-3-methylbut-2-enoic acid **3.17** (400 mg, 2.23 mmol, 1.0 equiv) was reacted with oxalyl chloride (250 µL, 2.91 mmol, 1.3 equiv), DMF (2 drops), 2-amino-4-phenylbutane (1.09 mL, 6.70 mmol, 3.0 equiv) and aq. NaOH (1M, 18 mL, 18.00 mmol, 8.0 equiv) in DCM (18 mL) overnight. The crude product was purified by flash chromatography (eluent: CyHex/EtOAc/Et_3N 90:10:2) to afford 2-Bromo-3-methyl-*N*-(4-phenylbutan-2-yl)but-2-enamide **3.19k** (495 mg 1.60 mmol, 72%) as a white solid

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.57 – 7.07 (m, 5H), 5.89 (d, J = 6.9 Hz, 1H), 4.25 – 3.94 (m, 1H), 2.83 – 2.57 (m, 2H), 2.09 (s, 3H), 1.96 (s, 3H), 1.93 – 1.71 (m, 2H), 1.32 – 0.99 (d, J= 10.8, 3H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** δ = 168.8, 136.2, 131.2, 129.6 (2 C), 129.5 (2 C),

128.7, 128.3, 50.9, 45.2, 34.4, 23.8, 21.8, 19.5. **IR (neat):** ν = 3277, 2929, 2850, 1629 cm^{-1}. **MS (EI, 70 eV, 200 °C):** m/z (%) = 309.1 $[M]^{+\cdot}$. **Melting point:** 77-79 °C

2-Bromo-3-methyl-*N*-(4-phenylbutan-2-yl)-*N*-((2-(trimethylsilyl)ethoxy)methyl)but-2-enamide 3.13k

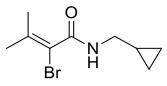


Chemical Formula: $C_{21}H_{34}BrNO_2Si$
Exact Mass: 439,1542

Following general procedure **C,** 2-bromo-3-methyl-*N*-(4-phenylbutan-2-yl)but-2-enamide **3.19k** (200 mg, 0.65 mmol, 1.0 equiv) was reacted with NaHMDS (258 µL, 1.29 mmol, 2.0 equiv), 2-(trimethylsilyl)ethoxymethyl chloride (229 µL, 1.29 mmol, 2.0 equiv) in THF (2 mL). The crude product was purified by flash chromatography (eluent: CyHex/EtOAc/Et_3N 90:10:2) affording 2-Bromo-3-methyl-*N*-(4-phenylbutan-2-yl)-*N*-((2-(trimethylsilyl)ethoxy)methyl)but-2 enamide **3.13k** (201 mg 0.47 mmol, 73% yield) as a colorless oil

^{1}H NMR ($CDCl_3$, 300 MHz, mixture of two conformers, ratio = 0.60/0.40): δ = 7.51 – 6.77 (m, 5H), 5.10 – 4.83 (m, 1H), 4.80-4.30 (m, 2H), 3.99– 3.31 (m, 2H), 2.87 – 2.38 (m, 2H), 2.15-1.6 (m, 8H), 1.40-1.20 (m, 3H), 0.99 – 0.79 (m, 2H), 0.00 (s, 9H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** complex mixture of rotamers. **IR (neat):** ν = 2950, 1645 cm^{-1}. **MS (EI, 70 eV, 200 °C):** m/z (%) = 439.5 $[M]^{+\cdot}$

2-Bromo-N-(cyclopropylmethyl)-3-methylbut-2-enamide 3.19l



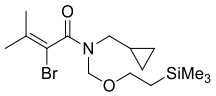
Chemical Formula: $C_9H_{14}BrNO$
Exact Mass: 231,0259

Following general procedure **B**, 2-bromo-3-methylbut-2-enoic acid **3.17** (500 mg, 2.79 mmol, 1.0 equiv) was reacted with oxalyl chloride (311 µL, 3.63 mmol, 1.3 equiv), DMF (2 drops), aminomethylcyclopropane (1.45 mL, 16.76 mmol, 6.0 equiv) and aq. NaOH (1M, 22 mL, 22 mmol, 8.0 equiv) in DCM (22 mL). The crude product was purified by flash chromatography (eluent: CyHex/EtOAc/Et_3N 90:10:2) affording 2-Bromo-*N*-(cyclopropylmethyl)-3-methylbut-2-enamide **3.19l** (467 mg, 2.01 mmol, 72%) as a yellow solid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.6-6.2 (s, 1H), 2.91 (m, 2H), 1.81 (s, 3H), 1.71 (s, 3H), 0.98 – 0.57 (m, 1H), 0.38 – 0.13 (m, 2H), 0.07 – 0.00 (m, 2H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** δ

= 164.9, 141.1, 110.9, 44.5, 25.6, 22.4, 10.5, 3.3 (2 C). **IR (neat):** ν = 3273, 2917, 1625 cm^{-1}. **MS (EI, 70 eV, 200 °C):** m/z (%) = 232.3 $[M]^{+\cdot}$. **Melting point:** 75-77 °C

2-Bromo-*N*-(cyclopropylmethyl)-3-methyl-*N*-((2-(trimethylsilyl)ethoxy)methyl)but-2-enamide 3.13l

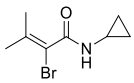


Chemical Formula: $C_{15}H_{28}BrNO_2Si$
Exact Mass: 361,1073

Following general procedure **C**, 2-bromo-*N*-(cyclopropylmethyl)-3-methylbut-2-enamide **3.19l** (200 mg, 0.86 mmol, 1.0 equiv) was reacted with NaHMDS (345 µL, 1.72 mmol, 2.0 equiv) and 2 (trimethylsilyl)ethoxymethyl chloride (306 µL, 1.72 mmol, 2.0 equiv) in THF (3 mL). The crude product was purified by flash chromatography (eluent: CyHex/EtOAc/Et_3N 90:10:2) affording 2-Bromo-*N*-(cyclopropylmethyl)-3-methyl-*N*-((2-(trimethylsilyl)ethoxy)methyl)but-2-enamide **3.13l** (240 mg, 0.66 mmol, 77%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.05 – 4.54 (m, 2H), 3.48 – 3.28 (m, 2H), 3.28 – 3.03 (m, 2H), 1.79 (s, 3H), 1.75 – 1.64 (m, 3H), 1.05 – 0.70 (m, 3H), 0.48 – 0.31 (m, 2H), 0.23 – 0.04 (m, 2H), -0.08 – -0.17 (m, 9H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz, major rotamers):** δ = 166.5, 136.0, 107.6, 78.2, 72.8, 65.5, 47.5, 22.9, 21.6, 17.9, 9.3, 3.4, -1.5. **IR (neat):** ν = 2952, 1648 cm^{-1}. **MS (EI, 70 eV, 200 °C):** m/z (%) = 361.5 $[M]^{+\cdot}$

2-Bromo-*N*-cyclopropyl-3-methylbut-2-enamide 3.19m



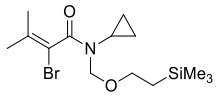
Chemical Formula: $C_8H_{12}BrNO$
Exact Mass: 217,0102

Following general procedure **B**, 2-bromo-3-methylbut-2-enoic acid **3.17** (500 mg, 2.79 mmol, 1 equiv) was reacted with oxalyl chloride (311 µL, 3.63 mmol, 1.3 equiv), DMF (2 drops), cyclopropylamine (1.16 mL, 16.76 mmol, 6.0 equiv) and aq. aq. NaOH (1M, 22 mL, 22 mmol, 8.0 equiv) in DCM (22 mL). The crude product was purified by flash chromatography (eluent: CyHex/EtOAc/Et_3N 90:10:2) affording 2-Bromo-*N*-cyclopropyl-3-methylbut-2-enamide **3.19m** (463 mg, 2.12 mmol, 76%) as a yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.34 (s, 1H), 2.82-2.62 (m, 1H), 2.11 (s, 3H), 1.96 (s, 3H), 0.99 – 0.72 (m, 2H), 0.68 – 0.49 (m, 2H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** δ = 166.0, 143.7,

110.6, 26.4, 23.0, 22.8, 6.6 (2 C). **IR (neat):** ν = 3277, 2930, 2860, 1517 cm^{-1}. **MS (EI, 70 eV, 200 °C):** m/z (%) = 217.1 $[M]^{+\cdot}$

2-Bromo-*N*-cyclopropyl-3-methyl-*N*-((2-(trimethylsilyl)ethoxy)methyl)but-2-enamide 3.13m

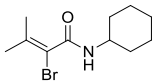


Chemical Formula: $C_{14}H_{26}BrNO_2Si$
Exact Mass: 347,0916

Following general procedure **C**, 2-bromo-*N*-cyclopropyl-3-methylbut-2-enamide **3.19m** (200 mg, 0.92 mmol, 1.0 equiv) was reacted with NaHMDS (367 µL, 1.83 mmol, 2.0 equiv), 2 (trimethylsilyl)ethoxymethyl chloride (325 µL, 1.83 mmol, 2.0 equiv) in THF (3 mL). The crude product was purified by flash chromatography (eluent: CyHex/EtOAc/Et_3N 90:10:2) affording 2-Bromo-*N*-cyclopropyl-3-methyl-*N*-((2-(trimethylsilyl)ethoxy)methyl)but-2-enamide **3.13m** (256 mg, 0.73 mmol, 80%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.77 (m, 2H), 3.78 – 3.41 (m, 2H), 2.79 (m, 1H), 1.95-1.85 (s, 3H), 1.85-1.75 (s, 3H), 1.02 – 0.6 (m, 6H), 0.01 (s, 9H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** δ = 170.9, 136.8, 110.9, 80.9, 76.8, 67.3, 31.1, 24.6, 23.3, 19.5, 8.2, 0.0 (3 C). **IR (neat):** ν = 2950, 1652 cm^{-1}. **MS (EI, 70 eV, 200 °C):** m/z (%) = 347.3 $[M]^{+\cdot}$

2-Bromo-*N*-cyclohexyl-3-methylbut-2-enamide 3.19n

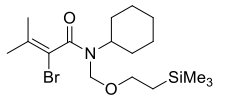


Chemical Formula: $C_{11}H_{18}BrNO$
Exact Mass: 259,0572

Following general procedure **B**, 2-bromo-3-methylbut-2-enoic acid **3.17** (500 mg, 2.79 mmol, 1.0 equiv) was reacted with oxalyl chloride (311 µL, 3.63 mmol, 1.3 equiv), DMF (2 drops), cyclohexanamine (1.19 mL, 16.76 mmol, 6.0 equiv) and aq. NaOH (1M, 22 mL, 22 mmol, 8.0 equiv) in DCM (22 mL). The crude product was purified by flash chromatography (eluent: CyHex/EtOAc/Et_3N 90:10:2) affording 2-Bromo-*N*-cyclohexyl-3-methylbut-2-enamide **3.19n** (661 mg, 2.54 mmol, 91%) as a white solid. **^{1}H NMR ($CDCl_3$, 300 MHz):** δ = 6.07 (s, 1H), 3.85 – 3.61 (m, 1H), 2.02 (s, 3H), 1.90 (s, 3H), 1.90-1.8 (m, 2H), 1.76 – 1.52 (m, 3H), 1.44 – 1.25 (m, 2H), 1.25 – 1.08 (m, 3H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** δ = 163.9, 142.0, 111.2, 48.7, 32.7, 26.0, 25.5, 24.7(2 C), 22.6 (2 C).

IR (neat): ν = 3281, 2935, 1546 cm^{-1}. **MS (EI, 70 eV, 200 °C):** m/z (%) = 259.1 $[M]^{+\cdot}$. **Melting point:** 71-73 °C

2-Bromo-*N*-cyclohexyl-3-methyl-*N*-((2-(trimethylsilyl)ethoxy)methyl)but-2-enamide 3.13n



Chemical Formula: $C_{17}H_{32}BrNO_2Si$
Exact Mass: 389,1386

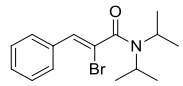
Following general procedure **C**, 2-bromo-*N*-cyclohexyl-3-methylbut-2-enamide **3.19n** (200 mg, 0.769 mmol, 1.0 equiv) was reacted with NaHMDS (309 µL, 1.54 mmol, 2.0 equiv), 2-(trimethylsilyl)ethoxymethyl chloride (273 µL, 1.54 mmol, 2.0 equiv) in THF (2 mL). The crude product was purified by flash chromatography (eluent: CyHex/EtOAc/Et_3N 90:10:2) affording 2-Bromo-*N*-cyclohexyl-3-methyl-*N*-((2-(trimethylsilyl)ethoxy)methyl)but-2-enamide **3.13n** (267 mg, 0.684 mmol, 89% yield) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz,): δ = 4.97 – 4.5 (m, 2H), 4.13 (m, 1H), 3.67 – 3.54 (m, 1H), 3.47 – 3.35 (m, 1H), 1.90 (m, 3H), 1.84-.1.70 (m, 6H), 1.68 – 1.00 (m, 7H), 1.01 – 0.81 (m, 2H), 0.00 (s, 9H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** δ = 168.5, 137.2, 109.6, 77.4, 71.6, 67.3, 66.6, 66.3, 60.1, 55.5, 27.3, 26.9–26.7, 24.4–23.2, 19.6, 0.0 (3 C). **IR (neat):** ν = 2930, 2854, 1646 cm^{-1}. **MS (EI, 70 eV, 200 °C):** m/z (%) = 389.1 $[M]^{+\cdot}$

(*Z*)-2-Bromo-*N*,*N*-diisopropyl-3-phenylacrylamide 3.13o and (*E*)-2-bromo-*N*,*N*-diisopropyl-3-phenylacrylamide 3.13p

An isomeric mixture of *E*/*Z*-2-bromo-3-phenylideneprop-2-enoic acid (1.17 g, 5.18 mmol, 1.0 equiv) was reacted with thionyl chloride (2.50 mL, 34.5 mmol, 6.7 equiv) at 80 °C for 45 min. Then, all volatiles were evaporated under high vacuum and the resulting yellow liquid was taken up in DCM (15 mL) and cooled to 0 °C. Et_3N (0.86 mL, 6.21 mmol, 1.2 equiv) and diisopropylamine (1.46 mL, 10.4 mmol, 2 equiv) were added, the reaction mixture was allowed to warm up to rt and was stirred overnight. After quenching with sat. solution of NH_4Cl, the aq. phase was extracted three times with DCM. The unified org. phase was washed with brine, dried over Na_2SO_4 and was concentrated under reduced pressure. From the crude mixture, the two isomers were isolated by column chromatography (4% to 10% EtOAc in CyHex) giving (Z)-2-Bromo-*N*,*N*-diisopropyl-3-phenylacrylamide **3.13o** (550 mg, 1.77 mmol, 34 %) and E)-2-bromo-*N*,*N*-diisopropyl-3-phenylacrylamide **3.13p** (385 mg, 1.24 mmol, 24 %).

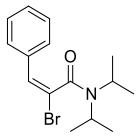
(*Z*)-2-Bromo-*N*,*N*-diisopropyl-3-phenylacrylamide 3.13o



Chemical Formula: $C_{15}H_{20}BrNO$
Exact Mass: 309,0728

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.71 - 7.64 (m, 2 H), 7.43 - 7.30 (m, 3 H), 6.96 (s, 1 H), 4.41 – 3.96 (m, 1 H), 3.70 - 3.24 (m, 1 H), 1.63 - 1.10 (m, 12 H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** δ =166.0, 134.1, 129.0, 128.7, 128.3, 115.9, 51.3, 45.9, 20.2 (4 C). **IR (neat):** ν = 2972, 2931, 1627, 763, 684cm^{-1}. **MS (EI, 70 eV, 200 °C):** m/z (%) = 309.2 $[M]^{+\cdot}$. **Mp:** 62-64°C

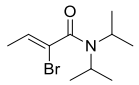
(*E*)-2-Bromo-*N*,*N*-diisopropyl-3-phenylacrylamide 3.13p



Chemical Formula: $C_{15}H_{20}BrNO$
Exact Mass: 309,0728

^{1}H NMR ($CDCl_3$, 300 MHz): δ =7.43 - 7.34 (m, 2 H), 7.34 - 7.21 (m, 3 H), 6.92 (s, 1 H), 4.07 (sept, *J*=6.7 Hz, 1 H), 3.34 (sept, *J*=6.8 Hz, 1 H), 1.46 (dd, *J*=6.6, 1.0 Hz, 6 H), 1.17 (d, *J*=6.6 Hz, 3 H), 0.66 (d, *J*=6.8 Hz, 3 H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** δ = 164.9, 134.7, 131.7, 128.5, 127.8, 115.1, 51.3, 45.9, 20.4, 20.1, 19.8, 19.6. **IR (neat):** ν = 2968, 2930, 1625, 751, 669cm^{-1}. **MS (EI, 70 eV, 200 °C):** m/z (%) = 309.2 $[M]^{+\cdot}$. **Mp:** 62-64°C

(*Z*)-2-Bromo-*N*,*N*-diisopropylbut-2-enamide 3.13q

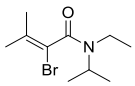


Chemical Formula: $C_{10}H_{18}BrNO$
Exact Mass: 247,0572

Following general procedure **B**, (2*Z*)-2-bromobut-2-enoic acid (400 mg, 2.42 mmol, 1.2 equiv) was reacted with oxalyl chloride (0.21 mL, 2.42 mmol, 1.2 equiv), DMF (2 drops), diisopropylamine (0.29 mL, 2.02 mmol, 1.0 equiv) and NaOH (1 M, 21 mL, 21 mmol, 10.4 equiv) in DCM (21 mL). The crude product was purified by flash chromatography (eluent: 0% to 5% EA in CyHex) affording (Z)-2-Bromo-*N*,*N*-diisopropylbut-2-enamide **3.13q** (432 mg, 1.74 mmol, 86 %) as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz, mixture of two conformers, ratio = 0.75/0.25): δ = 6.05 and 4.30 (2 q, *J*=6.6 Hz and *J*=7.1 Hz, together 1 H), 4.30-3.11 (m, 2 H), 1.80 (d, *J*=6.6 Hz, 3 H), 1.52 - 1.02 (m, 12 H). **^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz, major rotamer):** δ = 165.9, 126.6, 119.2, 50.7, 46.0, 20.8, 20.4, 20.1, 16.4, 14.1. **IR(neat) ν:** 2969, 2933, 1737, 1632, 1328 cm^{-1}. **LRMS (EI)** calcd for $C_{10}H_{18}BrNO$ ($[M]^{+\cdot}$): 247.1; found: 247.1;

2-bromo-*N*-ethyl-*N*-isopropyl-3-methylbut-2-enamide 3.13r

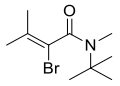


Chemical Formula: $C_{10}H_{18}BrNO$
Exact Mass: 247,0572

Following general procedure **B**, 2-bromo-3-methylbut-2- enoic acid **3.17** (180 mg, 1.00 mmol, 1.0 equiv) was reacted with oxalyl chloride (111 µL, 1.31 mmol, 1.3 equiv), DMF (2 drops), ethyl(propan-2-yl)amine (175 mg, 2.00 mmol, 2.0 equiv) and aq. NaOH (1M, 8 mL, 8.00 mmol, 8.0 equiv) in DCM (8 mL). The crude product was purified by flash chromatography (gradient 0% to 10% EtOAc in CyHex) affording 2-bromo-*N*-ethyl-*N*-isopropyl-3-methylbut-2-enamide **3.13r** (240 mg, 0.97 mmol, 96%).as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz, mixture of two conformers, ratio = 0.79/0.21): δ = 3.90- 4.40 (m, 1H), 3.43 – 2.91 (m, 2H), 1.74 (s, 3H), 1.65 (s, 3H), 1.18 – 0.87 (m, 9H) ppm. **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** δ = 165.8, 134.7, 108.8, 50.5, 46.6, 35.4, 22.8, 21.6, 20.6, 13.9 ppm. **IR (neat):** ν = 1420, 1627, 2956 cm^{-1}. **MS (EI, 70 eV, 200 °C):** m/z (%) = 247.2 (1.6) [M+.]

2-Bromo-*N*-(*tert*-butyl)-*N*,3-dimethylbut-2-enamide 3.13s



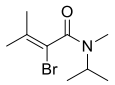
Chemical Formula: $C_{10}H_{18}BrNO$
Exact Mass: 247,0572

Following general procedure **B**, 2-bromo-3-methylbut-2-enoic acid **3.17** (500 mg, 2.79 mmol, 1.0 equiv) was reacted with oxalyl chloride (288 µL, 3.35 mmol, 1.2 equiv), DMF (2 drops) 2-bromo-*N*-(*tert*-butyl)-*N*,3-dimethylbut-2-enamide (2.07 g, 16.76 mmol, 6.0 equiv) and aq. NaOH (1M, 29 mL, 29.00 mmol, 10.4 equiv) in DCM (29 mL). The crude product was purified by flash chromatography (eluent: CyHex/EtOAc/Et_3N 90:10:2) affording 2-Bromo-N-(tert-butyl)-N,3-dimethylbut-2-enamide **3.13s** (385 mg, 1.54 mmol, 55%) as a yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.92 (s, 3H), 1.87 (s, 3H), 1.80 (s, 3H), 1.45 (s, 9H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** δ =167.3, 133.3, 111.7, 57.0, 33.3, 27.9, 23.0, 21.1.

IR (neat): ν = 2920, 1665, 1400, 1260 cm^{-1}. **HRMS(ESI):** calcd for $C_{10}H_{19}BrNO$ ($[M+H]^+$) : 248.0648; found: 248.0645;

2-Bromo-*N*-isopropyl-*N*,3-dimethylbut-2-enamide 3.13t

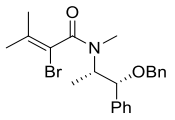


Chemical Formula: $C_9H_{16}BrNO$
Exact Mass: 233,0415

Following general procedure **B**, 2-bromo-3-methylbut-2-enoic acid **3.17** (500 mg, 2.79 mmol, 1.0 equiv) was reacted with oxalyl chloride (312 µL, 3.63 mmol, 1.3 equiv), DMF (2 drops), methyl(propan-2-yl)amine (729 µL, 6.90 mmol, 2.5 equiv) and aq. NaOH (1 M, 22 mL, 22.3 mmol, 8.0 equiv) in DCM (22 mL) for 12 hours. The crude product was purified by flash chromatography (eluent: CyHex/EtOAc/Et_3N 90:10:2) affording 2-Bromo-*N*-isopropyl-N,3-dimethylbut-2-enamide **3.13t** (580 mg 2.47 mmol, 89%) as a slightly yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz, mixture of rotamers): δ = 4.78 – 3.83 (m, 1H), 2.73 – 2.64 (m, 3H), 1.82 – 1.72 (m, 3H), 1.70 – 1.62 (m, 3H), 1.13 – 1.03 (m, 3H), 1.03 – 0.97 (m, 3H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz, mixture of rotamers):** δ = 166.1, 166.0, 134.6, 134.2, 108.9, 108.1, 49.7, 47.6, 43.9, 42.3, 28.7, 26.2, 25.4, 25.3, 24.3, 22.7, 22.6, 21.4, 21.3, 20.9, 20.5, 20.0, 19.7, 19.0, 18.7. **IR (neat):** ν = 2980, 1645 cm^{-1}. **HRMS(ESI):** calcd for $C_9H_{17}BrNO$ ($[M+H]^+$): 234.0494; found: 234.0490;

***N*-((1*R*,2*S*)-1-(Benzyloxy)-1-phenylpropan-2-yl)-2-bromo-N,3-dimethylbut-2-enamide 3.13u**



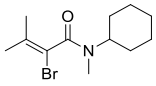
Chemical Formula: $C_{22}H_{26}BrNO_2$
Exact Mass: 415,1147

To a solution of 2-bromo-3-methylbut-2-enoic acid **3.17** (500 mg, 2.79 mmol, 1.0 equiv) and DIPEA (1.38 mL, 8.38 mmol, 3.0 equiv) in DCM (28 mL) at 0 °C, PyBOP (1.45 g, 2.79 mmol, 1.0 equiv) was added in one portion and stirred 20 min at 0 °C. (1*R*,2*S*)-1-(benzyloxy)-*N*-methyl-1-phenylpropan-2-amine (713 mg, 2.79 mmol, 1.0 equiv) was then added in one portion at 0 °C. The resulting mixture was stirred at room temperature during 16 hours. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$. The resulting mixture was extracted three times with ethyl acetate and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated in Vacuo.

Purification by column chromatography (SiO_2, pentane/ AcOEt, 9/1 to 1/1 affording *N*-((1*R*,2*S*)-1-(Benzyloxy)-1-phenylpropan-2-yl)-2-bromo-N,3-dimethylbut-2-enamide **3.13u** (942 mg, 2.26 mmol, 81 %) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz, complex mixture of rotamers): δ = 7.46 – 7.06 (m, 10H), 4.81 – 3.88 (m, 4H), 3.07 – 2.59 (m, 3H), 2.01 – 1.48 (m, 4H), 1.36 – 0.97 (m, 6H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** δ = 166.5, 139.1, 138.9, 138.2, 134.5, 128.8, 128.4, 128.4, 128.3, 127.8, 127.7, 127.6, 126.8, 83.5, 83.3, 77.4, 70.9, 68.3, 60.3, 59.5, 54.0, 31.9, 28.8, 22.7, 21.6, 20.4, 20.3, 14.2, 13.4, 12.9, 12.8, 11.8, 11.7. **HRMS(ESI):** calcd for $C_{22}H_{27}BrNO_2$ ($[M+H]^+$): 416.1225; found: 416.1231; **IR(neat) ν:** 2932, 2866, 1690, 1650, 1512, 1254 cm^{-1}.

2-Bromo-*N*-cyclohexyl-*N*,3-dimethylbut-2-enamide 3.13v

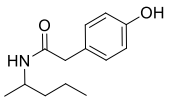


Chemical Formula: $C_{12}H_{20}BrNO$
Exact Mass: 273,0728

Following general procedure **B**, 2-bromo-3-methylbut-2-enoic acid **3.17** (600 mg, 3.35 mmol, 1.0 equiv) was reacted with oxalyl chloride (375 µL, 4.35 mmol, 1.3 equiv), DMF (2 drops), *N*-methylcyclohexanamine (947 µL, 6.70 mmol, 6.0 equiv) and aq. NaOH (1 M, 26 mL, 26 mmol, 8.0 equiv) in DCM (27 mL) for 12 hours. The crude product was purified by flash chromatography (eluent: CyHex/EtOAc/Et_3N 90:10:2) affording 2-Bromo-*N*-cyclohexyl-*N*,3-dimethylbut-2-enamide **3.13v** (643 mg, 2.35 mmol, 70%) as a slightly yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz, mixture of rotamers): δ = 4.23 – 3.30 (m, 1H), 2.68 – 2.58 (m, 3H), 1.74 – 1.66 (m, 3H), 1.65 – 1.54 (m, 5H), 1.52 – 0.77 (m, 8H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz, mixture of rotamers):** δ =165.9, 134.3, 133.8, 108.9, 108.0, 58.1, 51.9, 30.8, 29.9, 29.8, 29.1, 26.6, 25.4, 25.1, 25.1, 24.8, 22.5, 22.3, 21.2, 20.7. **IR (neat):** ν = 2945, 1390 cm^{-1} **HRMS(ESI):** calcd for $C_{12}H_{20}BrNaNO$ ($[M+Na]^+$): 296.0620; found: 296.0623;

2-(4-Hydroxyphenyl)-*N*-(pentan-2-yl)acetamide 3.40



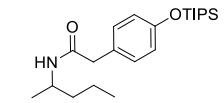
Chemical Formula: $C_{13}H_{19}NO_2$
Exact Mass: 221,1416

To a stirred solution of pentan-2-amine (5.73 g, 65.7 mmol, 1.0 equiv), 4-hydroxyphenylacetic acid (10 g, 65.7 mmol, 1.0 equiv) and DIPEA (13.0 mL, 78.9 mmol, 1.2 equiv) in DMF (500 mL) was added EDCI (12.2 g, 78.9 mmol, 1.2 equiv) in one portion at 0°C.

The reaction was stirred at 0°C for 1 h and 2 h at room temperature. The reaction was quenched by adding 50 mL of HCl (1 N). The aq. phase was extracted with DCM (2 x 50 mL), then the org. phase was washed with an sat. aq. solution of $NaHCO_3$ (2x150 mL) and dried over $MgSO_4$, before being concentrated. The crude product was purified by flash chromatography (gradient: 30% to 65% EtOAc in CyHex) affording 2-(4-Hydroxyphenyl)-*N*-(pentan-2-yl)acetamide **3.40** (9.63 g, 43.52 mmol, 66%) as a white solid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.10-7.64 (m, 1 H), 7.04 (m , 2 H), 6.83 (m, 2 H), 5.35 (br. s., 1 H), 4.06 – 3.88 (m, 1 H), 3.49 (s, 2 H), 1.38 - 1.15 (m, 4 H), 1.04 (d, *J*=6.6 Hz, 3 H), 0.85 (t, *J*=7.0 Hz, 3 H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** δ = 172.2, 156.4, 130.6 (2C), 125.5, 116.3 (2C), 45.5, 43.0, 38.8, 20.8, 19.2, 14.0. **IR (neat):** ν = 3313, 2963, 2932, 2876, 1622, 1548, 1512, 1159 cm^{-1}. **Mp** = 105-106 °C. **HRMS(ESI):** calcd for $C_{13}H_{20}NO_2$ ($[M+H]^+$) : 222.1494; found: 222.1493;

***N*-(Pentan-2-yl)-2-(4-((triisopropylsilyl)oxy)phenyl)acetamide 3.41**

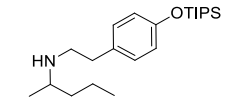


Chemical Formula: $C_{22}H_{39}NO_2Si$
Exact Mass: 377,2750

To a stirred solution of 2-(4-hydroxyphenyl)-*N*-(pentan-2-yl)acetamide **3.40** (1.26 g, 5.69 mmol, 1.0 equiv), imidazole (775 mg, 11.40 mmol, 2.0 equiv) in DMF (20 mL) was added TIPSCl (1.58 mL, 7.40 mmol, 1.3 equiv) in one portion. The solution was stirred for 18 h at 20°C before being quenched with an sat. aq. solution of NH_4Cl (50 mL). The aq. phase was extracted with EtOAc (2 x 50 mL), washed with brine (2 x 75 mL) and dried over $MgSO_4$ before being concentrated. The crude product was purified by flash chromatography (gradient: 0% to 40% EtOAc in CyHex) affording *N*-(Pentan-2-yl)-2-(4-((triisopropylsilyl)oxy)phenyl)acetamide **3.41** (1.80 g, 4.75 mmol, 83%) as a yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.15 - 7.02 (m, 2 H), 6.92 - 6.80 (m, 2 H), 5.26 – 4.87 (m, 1 H),), 4.01 – 3.85 (m, 1 H), 3.47 (s, 2 H), 1.36 - 1.16 (m, 7 H), 1.09 (d, *J*=6.8 Hz, 18 H), 1.00 (d, *J*=6.4 Hz, 3 H), 0.84 (t, *J*=7.0 Hz, 3 H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** δ = 170.8, 155.5, 130.6 (2C), 127.7, 120.7 (2C), 45.1, 43.4, 39.0, 20.9, 19.2, 14.0, 12.7 (3 C). **IR (neat):** ν = 3279, 2944, 2866, 1639, 1550, 1507, 1260 cm^{-1}**. HRMS(ESI):** calcd for $C_{22}H_{40}NO_2Si$ ($[M+H]^+$) : 378.2828; found: 378.2814;

_N_-(4-((Triisopropylsilyl)oxy)phenethyl)pentan-2-amine 3.42

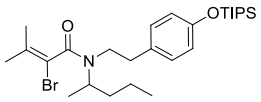


Chemical Formula: $C_{22}H_{41}NOSi$
Exact Mass: 363,2957

N-(pentan-2-yl)-2-(4-{[tris(propan-2-yl)silyl]oxy}phenyl)acetamide **3.41** (12.50 g, 33.0 mmol, 1.0 equiv) was dissolved in THF (75 mL) and BH_3•THF (1 M, 65.9 mL, 65.9 mmol, 2.0 equiv) was added dropwise at room temperature. The reaction mixture was refluxed for 5 h. After cooling it down to 0°C, the solution was quenched by adding first MeOH (20 mL) and then conc. H_2SO_4 (10 mL). The mixture was stirred at room temperature for 30 min before neutralization with an aq. solution of NaOH (4 M). The aq. phase was extracted with EtOAc, washed with water, dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (gradient: 0% to 5% NH_3 (7 M in MeOH) in DCM) affording *N*-(4-((Triisopropylsilyl)oxy)phenethyl)pentan-2-amine **3.42** (10.29 g, 28.3 mmol, 86%) as a yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ =7.10 – 6.97 (m, 2 H), 6.86- 6.71 (m, 2 H), 2.92 - 2.53 (m, 5 H), 1.43 - 1.19 (m, 8 H), 1.14 - 1.04 (m, 18 H), 1.00 (d, *J*=6.2 Hz, 3 H), 0.90 - 0.82 (m, 3 H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** δ = 154.3, 132.4, 129.5, 119.8, 52.8, 48.7, 39.4, 35.6, 20.3, 19.1, 17.9, 14.2, 12.6. **IR (neat):** ν = 2944, 2866, 1608, 1508, 1463, 1260 cm^{-1}. **HRMS(ESI):** calcd for $C_{22}H_{42}NOSi$ ($[M+H]^+$): 364.3036; found: 364.3026;

2-Bromo-3-methyl-*N*-(pentan-2-yl)-*N*-(4-((triisopropylsilyl)oxy)phenethyl)but-2-enamide 3.13w



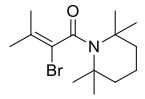
Chemical Formula: $C_{27}H_{46}BrNO_2Si$
Exact Mass: 523,2481

Oxalyl chloride (2.52 mL, 29.3 mmol, 1.3 equiv) was added to a solution of 2-bromo-3-methylbut-2-enoic acid **3.17** (5.25 g, 29.3 mmol, 1.3 equiv) in DCM (75 mL) at room temperature followed by DMF (52 µL, 676 µmol, 3 mol%). The resulting solution was stirred for 2 h (gas evolution stoped) at room temperature before being added to a solution of DIPEA (11.20 mL, 67.6 mmol, 3.0 equiv) and (pentan-2-yl)[2-(4-{[tris(propan-2-yl)silyl]oxy}phenyl)ethyl]amine **3.42** (8.20 g, 22.5 mmol, 1.0 equiv) in DCM (75 mL) stirred at 0°C. The reaction mixture was stirred for 15 h at room temperature. Then it was washed with HCl (1 N, 75 mL), a sat. aq. solution of $NaHCO_3$ (75 mL), dried over $MgSO_4$ and the solvent

was removed *in vacuo*. The crude product was purified by flash chromatography (gradient: 0% to 10% EtOAc in CyHex) affording 2-Bromo-3-methyl-*N*-(pentan-2-yl)-*N*-(4-((triisopropylsilyl)oxy)phenethyl)but-2-enamide **3.13w** (10.37 g , 19.77 mmol, 88%) as an orange oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.17 – 6.91 (m, 2 H), 6.86 - 6.71 (m, 2 H), 4.54 - 3.74 (m, 1 H), 3.53 - 3.14 (m, 2 H), 3.00 – 2.60 (m, 2 H), 2.01 – 1.72 (m, 6 H), 1.49 - 1.12 (m, 10 H), 1.12 - 1.04 (m, 18 H), 0.95 - 0.81 (m, 3 H), **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz, complex mixture of rotamers):** δ = 166.6, 166.4, 154.6, 154.3, 135.3, 134.5, 131.8, 130.7, 129.6, 129.2, 119.9, 119.6, 109.5, 109.0, 108.6, 54.5, 43.3, 43.2, 37.1, 36.4, 33.8, 33.5, 22.9, 22.8, 22.7, 21.9, 21.7, 21.6, 19.8, 19.5, 18.9, 17.8, 17.7, 13.9, 13.7, 12.9, 12.7, 12.5, 12.3, 12.1. **IR (neat):** ν = 2942, 2866, 1633, 1509, 1261 cm^{-1}. **HRMS(ESI):** calcd for $C_{27}H_{47}BrNO_2Si$ ($[M+H]^+$): 524.2559; found: 524.2517;

2-Bromo-3-methyl-1-(2,2,6,6-tetramethylpiperidin-1-yl)but-2-en-1-one 3.13x

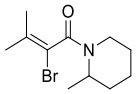


Chemical Formula: $C_{14}H_{24}BrNO$
Exact Mass: 301,1041

Following general procedure **B**, 2-bromo-3-methylbut-2-enoic acid **3.17** (500 mg, 2.79 mmol, 1.0 equiv) was reacted with oxalyl chloride (311 µL, 3.63 mmol, 1.3 equiv), DMF (2 drops), tretramethylpiperidine (2.85 mL, 16.76 mmol, 6.0 equiv) and aq. NaOH (1M, 22 mL, 22.00 mmol, 8.0 equiv) in DCM (22 mL). The crude product was purified by flash chromatography (eluent: CyHex/EtOAc/Et_3N 90:10:2) affording 2-Bromo-3-methyl-1-(2,2,6,6-tetramethylpiperidin-1-yl)but-2-en-1-one **3.13x** (735 mg, 2.43 mmol, 87%) as a yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.88 (2s, 3H each), 1.75 (m, 6H), 1.53 (s, 6H), 1.48 (s, 6H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** δ = 169.2, 134.2, 116.3, 57.7 (2 C), 39.4 (2 C) , 30.4 (2 C), 29.3(2 C), 24.4, 22.8, 15.3. **IR (neat):** ν = 2890, 2935, 3281 cm^{-1}. **MS (EI, 70 eV, 200 °C):** m/z (%) = 301.3 $[M]^{+\cdot}$

2-Bromo-3-methyl-1-(2-methylpiperidin-1-yl)but-2-en-1-one 3.13y

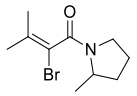


Chemical Formula: $C_{11}H_{18}BrNO$
Exact Mass: 259,0572

Following general procedure **B**, 2-bromo-3-methylbut-2-enoic acid **3.17** (3 g, 16.8 mmol, 1 equiv) was reacted with oxalyl chloride (1.87 mL, 21.8 mmol, 1.3 equiv), DMF (2 drops), 2-methylpiperidine (11.8 mL, 101 mmol, 6 equiv) and NaOH (1 M, 134 mL, 134 mmol, 8 equiv) in DCM (90 mL). The crude product was purified by flash chromatography (eluent: 0% to 20% EA in CyHex) affording 2-Bromo-3-methyl-1-(2-methylpiperidin-1-yl)but-2-en-1-one **3.13y** (3.565 g, 13.71 mmol, 82 %) as a colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz, mixture of two conformers, ratio = 0.55/0.45, 323 K): δ = 4.82 and 4.10 (2 m, together 1 H), 4.40 and 3.58 (2 m, together 1 H), 3.04 and 2.72 (2 m, together 1 H), 1.60 (m, 15 H). **^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz, , 323 K):** δ = 165.3, 165.1, 164.9, 134.6, 134.4, 108.8, 108.5, 108.3, 108.1, 50.3, 43.9, 43.7, 42.3, 41.9, 36.5, 31.4, 30.3, 29.8, 29.5, 26.6, 25.9, 25.4, 22.9, 22.8, 21.7, 21.5, 18.8, 17.1, 16.2, 15.7, 15.0. **IR (neat):** ν = 2986, 2935, 2863, 1626, 1422, 1272 cm^{-1}. **LRMS (EI)** calcd for $C_{11}H_{18}BrNO$ ($[M]^{+\cdot}$): 259.1; found: 259.1;

2-Bromo-3-methyl-1-(2-methylpyrrolidin-1-yl)but-2-en-1-oneone 3.13z



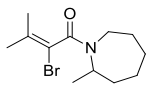
Chemical Formula: $C_{10}H_{16}BrNO$
Exact Mass: 245,0415

Following general procedure **B**, 2-bromo-3-methylbut-2-enoic acid **3.17** (750 mg, 4.19 mmol, 1 equiv) was reacted with oxalyl chloride (0.47 mL, 5.45 mmol, 1.3 equiv), DMF (2 drops), 2-methylpyrrolidine (1.22 mL, 12.6 mmol, 3 equiv) and NaOH (1 M, 33.5 mL, 33.5 mmol, 8 equiv) in DCM (34 mL). The crude product was purified by flash chromatography (eluent: 0% to 30% EA in CyHex) affording 2-Bromo-3-methyl-1-(2-methylpyrrolidin-1-yl)but-2-en-1-oneone **3.13z** (875 mg, 3.55 mmol, 85 %) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz, mixture of two conformers, ratio = 0.7/0.3, 298 K): δ = 4.03 – 3.62 (m, together 1H), 3.37 – 3.05 (m, together 2H), 1.87 – 1.63 (m, 3H), 1.63 – 1.57 (m, 3H), 1.54 (s, 3H), 1.44 – 1.29 (m, 1H), 0.93 (d, J = 6.4 Hz, together 3H).

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz, mixture of rotamers, major rotamer): δ = 164.0, 133.7, 109.4, 52.2, 46.9, 31.86, 23.39, 22.24, 20.55, 18.51. **IR (neat):** ν = 2960, 2935, 1640, 1443, 1253 cm^{-1}. **HRMS(ESI):** calcd for $C_{10}H_{16}BrNaNO([M+Na]^+)$: 268.0307; found: 268.0303;

2-Bromo-3-methyl-1-(2-methylazepan-1-yl)but-2-en-1-one 3.13aa



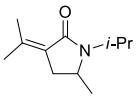
Chemical Formula: $C_{12}H_{20}BrNO$
Exact Mass: 273,0728

Following general procedure **B**, 2-bromo-3-methylbut-2-enoic acid **3.17** (750 mg, 4.19 mmol, 1 equiv) was reacted with oxalyl chloride (0.47 mL, 5.45 mmol, 1.3 equiv), DMF (2 drops), 2-methylazepan-1-ium chloride (2.25 g, 15 mmol, 3.6 equiv) and NaOH (1 M, 33.5 mL, 33.5 mmol, 8 equiv) in DCM (34 mL). The crude product was purified by flash chromatography (eluent: 0% to 30% EA in CyHex) affording 2-Bromo-3-methyl-1-(2-methylazepan-1-yl)but-2-en-1-one **3.13aa** (751 mg, 2.74 mmol, 65 %) as a colorless oil.

^1H NMR ($CDCl_3$, 300 MHz, complex mixture rotamers): δ = 4.28 – 2.28 (m, 3H), 1.94 – 0.58 (m, 17H). **$^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz, complex mixture of rotamers):** δ = 166.5, 166.3, 166.1, 165.9, 165.5, 165.1, 134.3, 134.0, 133.8, 133.5, 133.4, 108.7, 108.3, 108.1, 107.9, 77.4, 53.3, 53.0, 50.9, 50.0, 49.8, 48.4, 45.3, 42.9, 39.6, 39.2, 36.4, 36.0, 34.8, 29.5, 28.9, 27.9, 27.3, 26.6, 26.3, 24.8, 24.1, 23.9, 22.4, 22.3, 22.3, 21.6, 21.4, 20.4, 19.9, 19.5, 18.2, 17.8. **IR (neat):** ν = 2923, 2856, 1627, 1419 cm^{-1}. **HRMS(ESI):** calcd for $C_{12}H_{21}BrNO$ ($[M+H]^+$): 274.0801; found: 274.0804;

3.3. Scope of the C(sp^3)-H alkenylation

1-Isopropyl-5-methyl-3-(propan-2-ylidene)pyrrolidin-2-one 3.14a

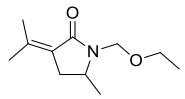


Chemical Formula: $C_{11}H_{19}NO$
Exact Mass: 181,1467

Following general procedure **A**, 2-bromo-*N*,*N*-diisopropyl-3-methylbut-2-enamide **3.13a** (50 mg, 0.19 mmol, 1.0 equiv) was reacted with cesium carbonate (93.2 mg, 0.29 mmol, 1.5 equiv), palladium allyl chloride (3.5 mg, 10 µmol, 5 mol%), PPh_3 (10.0 mg, 38 µmol, 20 mol%) and pivalic acid (6.8 mg, 57 µmol, 30 mol%) in mesitylene (1 mL) at 160°C overnight. The crude product was purified by preparative thin layer chromatography (eluent CyHex/EA 9:1) affording 1-Isopropyl-5-methyl-3-(propan-2-ylidene)pyrrolidin-2-one **3.14a** (26.3 mg, 0.14 mmol, 78 %) as a colorless oil. **^1H NMR ($CDCl_3$, 300 MHz):** δ = 4.15 (m, 1 H), 3.68 (m, 1 H),

2.85-2.65 (m, 1 H), 2.23 (s, 3 H), 2.23-2.15 (m, 1H), 1.73 (s, 3 H), 1.19-1.28 (m, 9 H). **$^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 75 MHz):** δ = 167.3, 136.9, 111.6, 48.0, 28.0, 27.9, 27.8, 24.1, 21.7, 19.9. **IR (neat):** ν = 2978, 2936, 1678, 1355 cm^{-1}. **HRMS(APCI):** calcd for $C_{11}H_{19}NO$ ($[M]^+$): 181.1467; found: 181.1453;

1-(Ethoxymethyl)-5-methyl-3-(propan-2-ylidene)pyrrolidin-2-one 3.14d

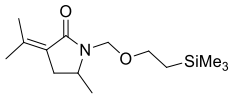


Chemical Formula: $C_{11}H_{19}NO_2$
Exact Mass: 197,1416

Following general procedure **A**, starting with 2-bromo-*N*-(ethoxymethyl)-*N*-isopropyl-3-methylbut-2-enamide **3.13d** (50.0 mg, 0.18 mmol, 1.0 equiv), was reacted with cesium carbonate (87.8 mg, 0.27 mmol, 1.5 equiv), palladium allyl chloride (3.3 mg, 9 µmol, 5 mol%.), Ethyldiphenylphosphine (7.7 mg, 36 µmol, 20 mol%.) and pivalic acid (5.5 mg, 54 µmol, 30 mol%) in mesitylene (1 mL) at 160°C overnight. The crude product was purified by preparative thin layer chromatography affording 1-(Ethoxymethyl)-5-methyl-3-(propan-2-ylidene)pyrrolidin-2-one **3.14d** (21.3 mg 0.11 mmol, 60%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.93 (d, J=10.8 Hz, 1 H), 4.64 (d, J=10.8 Hz, 1 H), 3.69 (m, 1H), 3.47 (m, 2 H), 2.85 (dd, J=15.6, 8.3 Hz, 1 H), 2.23 (s, 3 H), 2.17 (m, 1 H),), 1.75 (s, 3 H), 1.21 (d, J=6.2 Hz, 3 H), 1.14 (t, J=7.0 Hz, 3 H). **$^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 75 MHz):** δ = 169.8, 143.5, 123.6, 70.8, 63.8, 49.0, 33.5, 23.8, 21.1, 19.4, 15.2. **IR (neat):** ν = 2932, 1683, 1044 cm^{-1}. **HRMS(ESI):** calcd for $C_{11}H_{20}NNaO_2$ ($[M+Na]^+$): 220.1308; found: 220.1300;

5-Methyl-3-(propan-2-ylidene)-1-((2-(trimethylsilyl)ethoxy)methyl)-pyrrolidine-2-one 3.14e

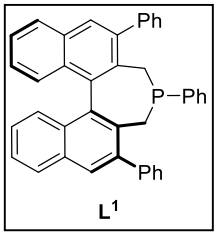


Chemical Formula: $C_{14}H_{27}NO_2Si$
Exact Mass: 269,1811

Racemic reaction: Following general procedure **A**, 2-bromo-*N*-isopropyl-3-methyl-*N*-((2-(trimethylsilyl)ethoxy)methyl)but-2-enamide **3.13e** (50.0 mg, 0.14 mmol, 1.0 equiv) was reacted with cesium carbonate (69.7 mg, 0.21 mmol, 1.5 equiv), palladium allyl chloride (2.6 mg, 7 µmol, 5 mol%.), PPh_3 (7.5 mg, 29 µmol, 20 mol%) and pivalic acid (4.4 mg, 42 µmol, 30 mol%.) in mesitylene (1 mL) at 160°C overnight. The crude product was purified by flash chromatography (gradient: CyHex to CyHex/EtOAc 90:10) affording 5-Methyl-3-(propan-2-

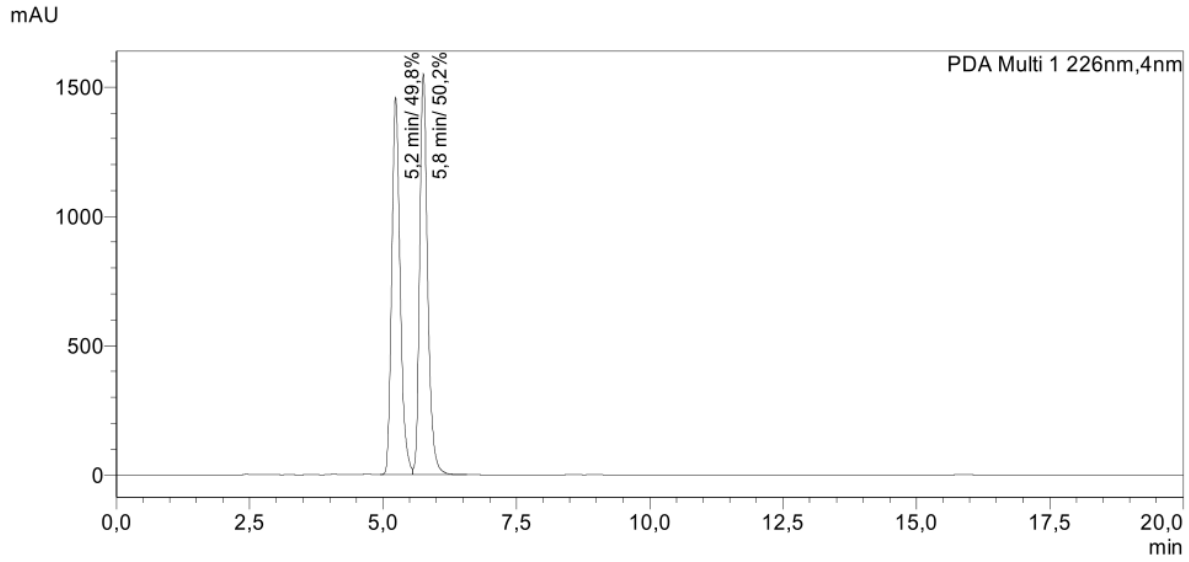
ylidene)-1-((2-(trimethylsilyl)ethoxy)methyl)-pyrrolidine-2-one **3.14e** (31.2 mg, 0.12 mmol, 81%) asa colorless oil.

Asymmetric catalysis: Following general procedure **A**, 2-bromo-*N*-isopropyl-3-methyl-*N*-((2-(trimethylsilyl)ethoxy)methyl)but-2-enamide **3.13e** (100.0 mg, 0.29 mmol, 1.0 equiv) was reacted with cesium carbonate (139.0 mg, 0.43 mmol, 1.5 equiv), palladium allyl chloride (2.6 mg, 7 µmol, 2.5 mol%.), phosphine[185] **L[1]** (15.4 mg, 29 µmol, 10 mol%) and pivalic acid (8.7 mg, 86 µmol, 30 mol%.) in mesitylene (2 mL) at 160°C overnight. The crude product was purified by flash chromatography (gradient: CyHex to CyHex/EtOAc 90:10) affording 5-Methyl-3-(propan-2-ylidene)-1-((2-(trimethylsilyl)ethoxy)methyl)-pyrrolidine-2-one **3.14e** (43.0 mg, 0.16 mmol, 56%) as a colorless oil.



L[1]

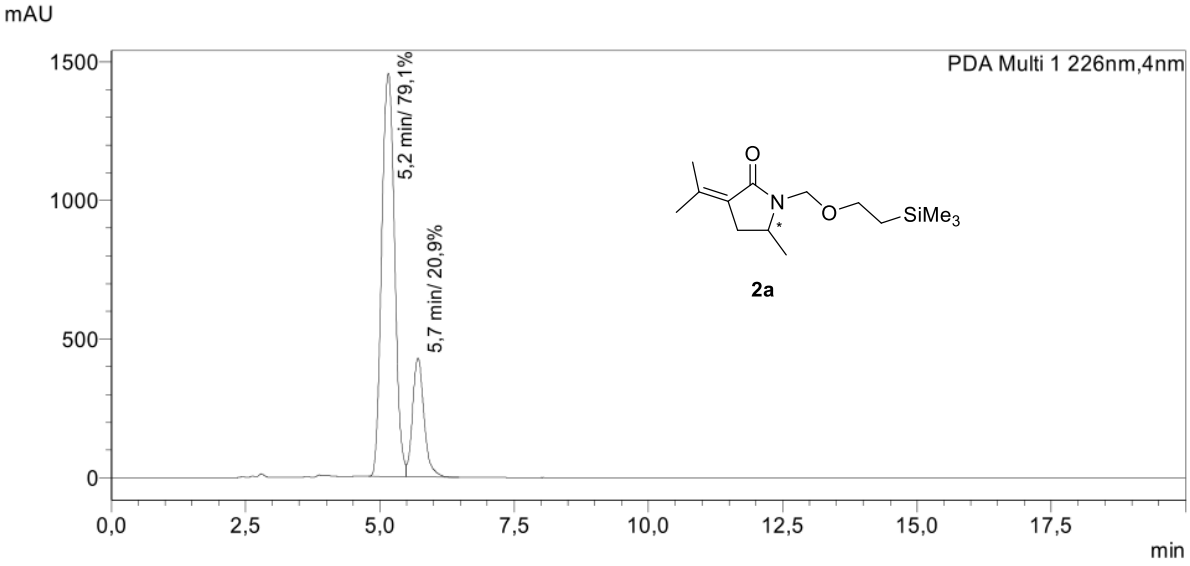
^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.96 (d, *J* = 10.6 Hz, 1H), 4.63 (d, *J* = 10.6 Hz, 1H), 3.78 – 3.66 (m, 1H), 3.59 – 3.42 (m, 2H), 2.92 – 2.80 (m, 1H), 2.31 – 2.23 (m, 3H), 2.23 – 2.13 (m, 1H), 1.78 (s, 3H), 1.24 (d, *J* = 6.3 Hz, 3H), 0.95 – 0.85 (m, 2H), -0.01 (s, 9H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** δ = 168.9, 142.4, 123.2, 69.8, 64.9, 48.4, 32.9, 23.2, 20.5, 18.8, 17.5, -1.7. **IR (neat):** ν = 2952, 1634, 1060 cm^{-1} **HRMS(ESI):** calcd for $C_{14}H_{27}NO_2Si$ ($[M]^+$): 270.1884; found: 270.1881; **HPLC separation:** Lux Cellulose 1, 4.6 x 150 mm; 99:1 (*n*-heptane/*i*-PrOH), 0.8 mL/min, 226 nm; t_r(major) = 5.2 min, t_r(minor) = 5.7 min, 79:21 e.r.



<Peak Table>

PDA Ch1 226nm

Peak#	Ret. Time	Area%	Resolution(USP)	Resolution(EMG(50%))
1	5,236	49,788	--	--
2	5,755	50,212	1,882	1,925
Total		100,000		

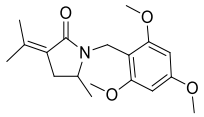


<Peak Table>

PDA Ch1 226nm

Peak#	Ret. Time	Area%	Resolution(USP)	Resolution(EMG(50%))
1	5,157	79,109	--	--
2	5,709	20,891	1,362	1,335
Total		100,000		

5-Methyl-3-(propan-2-ylidene)-1-(2,4,6-trimethoxybenzyl)pyrrolidin-2-one 3.14f

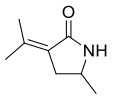


Chemical Formula: $C_{18}H_{25}NO_4$
Exact Mass: 319,1784

Following general procedure **A**, starting with 2-bromo-*N*-isopropyl-3-methyl-*N*-(2,4,6-trimethoxybenzyl)but-2-enamide **3.13f** (200.0 mg, 0.5 mmol, 1.0 equiv), was reacted with cesium carbonate (244 mg, 0.75 mmol, 1.5 equiv), palladium allyl chloride (9.3 mg, 0.025 mmol, 5 mol%.), PPh_3 (26 mg, 100 µmol, 20 mol%.) and pivalic acid (15 mg, 150 µmol, 30 mol%) in mesitylene (3.25 mL) at 160°C overnight. The crude product was purified by preparative thin layer chromatography affording 5-Methyl-3-(propan-2-ylidene)-1-(2,4,6-trimethoxybenzyl)pyrrolidin-2-one **3.14f** (100 mg, 0.31 mmol, 63 %) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.08 (s, 2H), 4.97 (d, J = 14.1 Hz, 1H), 4.13 (d, J = 14.1 Hz, 1H), 3.78 (s, 3H), 3.75 (s, 6H), 3.30 – 3.14 (m, 1H), 2.67 – 2.55 (m, 1H), 2.27 (t, J = 1.9 Hz, 3H), 2.12 – 2.04 (m, 1H), 1.70 (s, 3H), 1.08 (d, J = 6.2 Hz, 3H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** δ = 168.0, 160.9, 160.1, 139.8, 124.7, 105.1, 90.4, 55.8, 55.3, 48.6, 33.3, 32.6, 23.5, 20.7, 19.0. **IR (neat):** ν = 3054, 2968, 1689, 1658, 1265 cm^{-1} **HRMS(ESI):** calcd for $C_{18}H_{26}NO_4$ ($[M+H]^+$): 320.1856; found: 320.1861;

5-Methyl-3-(propan-2-ylidene)pyrrolidin-2-one 3.22

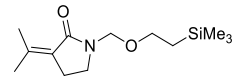


Chemical Formula: $C_8H_{13}NO$
Exact Mass: 139,0997

To a solution of 5-methyl-3-(propan-2-ylidene)-1-(2,4,6-trimethoxybenzyl)pyrrolidin-2-one **3.14f** (50 mg, 0.15 mmol, 1 equiv) in anisole (1.2 mL) was added TFA (2.5 mL, 34 mmol, 217 equiv). The mixture was stirred at room temperature until completion of the reaction (monitored by TLC). The crude mixture was evaporated under vaccum and the mixture was purified by colum chromatography eluant 1/1 pentane/EtOAc to pure EtOAc affording 5-Methyl-3-(propan-2-ylidene)pyrrolidin-2-one **3.22** (20.5 mg 0.15 mmol, 94 %) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.45 (s, 1H), 3.78 – 3.61 (m, 1H), 2.97 – 2.82 (m, 1H), 2.30 – 2.22 (m, 1H), 2.22 (s, 3H), 1.74 (s, 3H), 1.18 (d, J = 6.2 Hz, 3H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** δ = 171.9, 142.4, 123.8, 46.0, 35.3, 23.7, 23.5, 19.1. **IR (neat):** ν = 3172, 2924, 1685, 1653, 1437 cm^{-1}. **HRMS(ESI):** calcd for $C_8H_{14}NO$ ($[M+H]^+$): 140.1070; found: 140.1072;

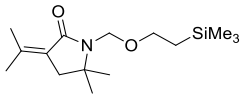
3-(Propan-2-ylidene)-1-((2-(trimethylsilyl)ethoxy)methyl)pyrrolidin-2-one 3.14g



Chemical Formula: $C_{13}H_{25}NO_2Si$
Exact Mass: 255,1655

Following general procedure **A**, 2-bromo-*N*-ethyl-3-methyl-*N*-((2-(trimethylsilyl)ethoxy)methyl)but-2-enamide **3.13g** (100 mg, 0.27 mmol, 1.0 equiv) was reacted with cesium carbonate (134 mg, 0.41 mmol, 1.5 equiv), palladium allyl chloride (5.0 mg, 13 µmol, 5 mol%), PPh_3 (14.4 mg, 55 µmol, 20 mol%) and pivalic acid (8.3 mg, 83 µmol, 30 mol%) in mesitylene (2 mL) at 160°C overnight. The crude product was analyzed by GC/MC analysis showing a ratio 14/86 desired product/dehalogenated by-product which is not purified.

5,5-Dimethyl-3-(propan-2-ylidene)-1-((2-(trimethylsilyl)ethoxy)methyl)pyrrolidin-2-one 3.14h

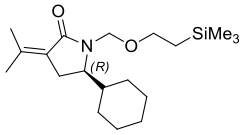


Chemical Formula: $C_{15}H_{29}NO_2Si$
Exact Mass: 283,1968

Following general procedure **A**, 2-bromo-*N*-(*tert*-butyl)-3-methyl-*N*-((2-(trimethylsilyl)ethoxy)methyl)but-2-enamide **3.13h** (100 mg, 0.27 mmol, 1.0 equiv) was reacted with cesium carbonate (134 mg, 0.41 mmol, 1.5 equiv), palladium allyl chloride (5.0 mg, 13 µmol, 5 mol%), PPh_3 (14.4 mg, 55 µmol, 20 mol%) and pivalic acid (8.3 mg, 83 µmol, 30 mol%) in mesitylene (2 mL) at 160°C overnight. The crude product was purified by flash chromatography (eluent: CyHex/EtOAc 90:10) affording 5,5-Dimethyl-3-(propan-2-ylidene)-1-((2-(trimethylsilyl)ethoxy)methyl)pyrrolidin-2-one **3.14h** (72 mg, 0.25 mmol, 92% yield) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.75 (s, 2H), 3.62 (m, 2H), 2.5 (s, 2H), 2.25 (s, 3H), 1.78 (s, 3H), 1.32 (s, 6H), 0.88 (m, 2H), 0.00 (s, 9H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** δ = 169.3, 143.4, 123.5, 69.2, 65.4, 56.40, 41.6, 30.3, 28.3, 23.8, 19.54, 18.3, -1.2. **IR (neat):** ν = 2945, 1688 cm^{-1}. **HRMS(ESI)** calcd for $C_{15}H_{29}NNaO_2Si$ ($[M+Na]^+$): 306.4818; found: 306.4807;

(*R*)-5-Cyclohexyl-3-(propan-2-ylidene)-1-((2-(trimethylsilyl)ethoxy)methyl)pyrrolidin-2-one 3.14i

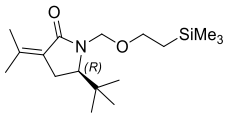


Chemical Formula: $C_{19}H_{35}NO_2Si$
Exact Mass: 337,2437

Following general procedure **A**, 2-bromo-*N*-(1-cyclohexylethyl)-3-methyl-*N*-((2-(trimethylsilyl)ethoxy)methyl)but-2-enamide **3.13i** (100 mg, 0.24 mmol, 1.0 equiv) was reacted with cesium carbonate (117 mg, 0.36 mmol, 1.5 equiv), palladium allyl chloride (4.4 mg, 12 µmol, 5 mol%), PPh_3 (12.5 mg, 48 µmol, 20 mol%) and pivalic acid (7.3 mg, 72 µmol, 30 mol%) in mesitylene (2 mL) at 160°C overnight. The crude product was purified by flash chromatography (eluent: CyHex/EtOAc 90:10) affording (R)-5-Cyclohexyl-3-(propan-2-ylidene)-1-((2-(trimethylsilyl)ethoxy)methyl)pyrrolidin-2-one **3.14i** (57 mg, 0.17 mmol, 70%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.00 (d, J = 5.5 Hz, 1H), 4.58 (d, J = 10.7 Hz, 1H), 3.66 – 3.37 (m, 2H), 2.53 (m, 1H), 2.25 (m, 2H), 1.91 (m, 1H), 1.84 (m, 2H), 1.81 (s, 3H), 1.67 (s, 3H), 1.59 – 0.82 (m, 10H), 0.01 (s, 9H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** δ = 170.1, 142.6, 123.9, 71.0, 65.5, 57.1, 38.9, 29.1, 26.6, 26.4, 26.1, 25.9, 24.3, 23.6, 19.2, 18.1, 0 (3 C). **IR (neat):** ν = 2952, 2823, 1618 cm^{-1}. **HRMS(ESI):** calcd for $C_{19}H_{35}NNaO_2Si$ ($[M+Na]^+$) : 360.2329; found: 360.2333; **Optical rotation:** $[\alpha]_D^{20}$ = -9.2 (c = 1.03, $CHCl_3$)

(*R*)-5-(*Tert*-butyl)-3-(propan-2-ylidene)-1-((2-(trimethylsilyl)ethoxy)methyl)pyrrolidin-2-one 3.14j



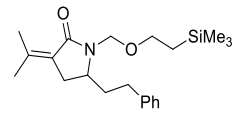
Chemical Formula: $C_{17}H_{33}NO_2Si$
Exact Mass: 311,2281

Following general procedure **A**, (*S*)-2-bromo-*N*-(3,3-dimethylbutan-2-yl)-3-methyl-*N*-((2-(trimethylsilyl)ethoxy)methyl)but-2-enamide **3.13j** (100.0 mg, 0.25 mmol, 1.0 equiv) was reacted with cesium carbonate (124 mg, 0.38 mmol, 1.5 equiv), palladium allyl chloride (4.7 mg, 13 µmol, 5 mol%), PPh_3 (13.4 mg, 51 µmol, 2 mol%) and pivalic acid (7.8 mg, 76 µmol, 30 mol%) in mesitylene (2 mL) at 160°C overnight. The crude product was purified by flash chromatography (eluent: CyHex/EtOAc 90:10) affording (R)-5-(Tert-butyl)-3-(propan-2-

ylidene)-1-((2-(trimethylsilyl)ethoxy)methyl)pyrrolidin-2-one **3.14j** (60.9 mg, 0.20 mmol, 77% yield) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.96 (d, J = 10.5 Hz, 1H), 4.75 (d, J = 10.5 Hz, 1H), 3.55 – 3.46 (m, 2H), 3.39 (dd, J = 8.9, 3.5 Hz, 1H), 2.67 – 2.52 (m, 1H), 2.52 – 2.40 (m, 1H), 2.23 (s, 3H), 1.78 (s, 3H), 0.93 – 0.89 (m, 11H), -0.02 (s, 9H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** δ = 171.8, 142.4, 124.3, 73.8, 65.6, 62.5, 35.8, 28.9, 26.4, 23.7, 19.5, 18.1, -1.3. **IR (neat):** ν = 1688, 2945 cm^{-1} **HRMS (ESI)** calcd for $C_{17}H_{33}NNaO_2Si$ ($[M+Na]^+$): 334.2172; found: 334.2166; **Optical rotation:** $[\alpha]_D^{20}$ = +21.3 (c = 1.02, $CHCl_3$).

5-Phenethyl-3-(propan-2-ylidene)-1-((2-(trimethylsilyl)ethoxy)methyl)pyrrolidin-2-one 3.14k

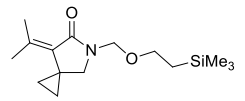


Chemical Formula: $C_{21}H_{33}NO_2Si$
Exact Mass: 359,2281

Following general procedure **A**, 2-bromo-3-methyl-*N*-(4-phenylbutan-2-yl)-*N*-((2-(trimethylsilyl)ethoxy)methyl)but-2-enamide **3.13k** (100 mg, 0.23 mmol, 1.0 equiv) was reacted with cesium carbonate (111 mg, 0.34 mmol, 1.5 equiv), palladium allyl chloride (4.2 mg, 12 µmol, 5 mol%), PPh_3 (11.9 mg, 45 µmol, 20mol%) and pivalic acid (6.9 mg, 68 µmol, 30 mol%) in mesitylene (2 mL) at 160°C overnight. The crude product was purified by flash chromatography (eluent: CyHex/EtOAc 90:10) affording 5-Phenethyl-3-(propan-2-ylidene)-1-((2-(trimethylsilyl)ethoxy)methyl)pyrrolidin-2-one **3.14k** (50 mg, 0.14 mmol, 61%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.35- 7.10 (m, 5H), 4.98 (d, J = 10.7 Hz, 1H), 4.66 (d, J = 10.7 Hz, 1H), 3.75-3.60 (m, 1H), 3.52 (m, 2H), 2.9-2.8 (m, 1H), 2.75 -2.5 (m, 2 H), 2,29 (s, 3H), 2.25-2.10 (m, 1 H), 1.82 (s, 3H), 1.5-1.15 (m, 2H), 1.02 – 0.78 (m, 2H), 0.00 (s, 9H) **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** δ = 171.1, 144.9, 142.7, 129.9 (2 C), 129.7 (2 C), 127.4, 124.8, 72.0, 66.9, 54.1, 36.9, 32.1 (2 C), 25.1, 20.7, 19.4, 0.0 (3 C). **IR (neat):** ν = 1688, 2945 cm^{-1}. **HRMS(ESI)** calcd for $C_{21}H_{33}NNaO_2Si$ ($[M+Na]^+$): 382.2173; found: 382.2162;

7-(Propan-2-ylidene)-5-((2-(trimethylsilyl)ethoxy)methyl)-5-azaspiro[2.4]heptan-6-one 3.14l

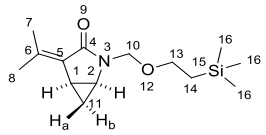


Chemical Formula: $C_{15}H_{27}NO_2Si$
Exact Mass: 281,1811

Following general procedure **A**, 2-bromo-*N*-(cyclopropylmethyl)-3-methyl-*N*-((2-(trimethylsilyl)ethoxy)methyl)but-2-enamide **3.13l** (200 mg, 0.55 mmol, 1.0 equiv) was reacted with cesium carbonate (269 mg, 0.83 mmol, 1.5 equiv), palladium allyl chloride (10.1 mg, 28 µmol, 5 mol%), PPh_3 (29 mg, 110 µmol, 20 mol%) and pivalic acid (17 mg, 165 µmol, 30 mol%) in mesitylene (4 mL) at 160°C overnight. The crude product was purified by flash chromatography (eluent: CyHex/EtOAc 90:10) affording 7-(Propan-2-ylidene)-5-((2-(trimethylsilyl)ethoxy)methyl)-5-azaspiro[2.4]heptan-6-one **3.14l** (82 mg, 0.29 mmol, 53% yield) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.75 (s, 2H), 3.59 – 3.41 (m, 2H), 3.21 (s, 2H), 2.23 (s, 3H), 1.62 (s, 3H), 1.40 (dt, *J* = 6.1, 3.1 Hz, 2H), 0.92 – 0.83 (m, 2H), 0.72 (q, *J* = 5.1 Hz, 2H), 0.02 – -0.10 (m, 9H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** δ = 169.9, 141.3, 126.2, 72.3, 65.5, 53.9, 21.8, 21.0, 20.3, 18.0, 14.8, -1.3. **IR (neat):** ν = 2952, 1689 cm^{-1}. **HRMS(ESI)** calcd for $C_{15}H_{27}NNaO_2Si$ ($[M+Na]^+$) : 304.1709; found: 304.1716;

4-(Propan-2-ylidene)-2-((2-(trimethylsilyl)ethoxy)methyl)-2-azabicyclo[3.1.0]hexan-3-one 3.14m



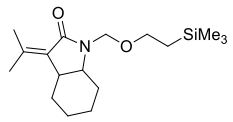
Chemical Formula: $C_{14}H_{25}NO_2Si$
Exact Mass: 267,1655

Following general procedure **A**, 2-bromo-*N*-cyclopropyl-3-methyl-*N*-((2-(trimethylsilyl)ethoxy)methyl)but-2-enamide **3.13m** (100 mg, 0.29 mmol, 1.0 equiv) was reacted with cesium carbonate (140 mg, 0.43 mmol, 1.5 equiv), palladium allyl chloride (5.8 mg, 15 µmol, 5 mol%), PPh_3 (15.1 mg, 57 µmol, 20 mol%) and pivalic acid (8.8 mg, 86 µmol, 30 mol%) in mesitylene (2 mL) at 160°C overnight. The crude product was purified by flash chromatography (eluent: CyHex/EtOAc 90:10) affording 4-(Propan-2-ylidene)-2-((2-(trimethylsilyl)ethoxy)methyl)-2-azabicyclo[3.1.0]hexan-3-one **3.14m** (53 mg, 0.20 mmol, 69% yield) as a colorless oil

The stereochemistry of the product was confirmed by NOE-spectroscopy.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.82 (d, J = 10.5 Hz, 1H, H_{10}), 4.73 (d, J = 10.5 Hz, 1H, H_{10}), 3.71 – 3.39 (m, 2H, H_{13}), 3.21 (ddd, *J* = 7.2, 5.0, 2.4 Hz, 1 H, H_2), 2.24 (s, 3H, H_7), 2.11 (m, 1H, H_1), 1.95 (s, 3H, H_8), 1.01-0.93 (m, 1 H, H_{11b}), 0.99-0.88 (m, 2 H, H_{15}), 0.43 (ddd, *J*=5.3, 4.5, 2.4 Hz, 1 H, H_{11a}), 0.0 (s, 9H, H_{16}). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** δ = 169.0 (C_4), 145.0 (C_6), 126.9 (C_5), 73.0 (C_{10}), 65.8 (C_{13}), 32.5 (C_2), 24.0 (C_8), 19.2 (C_7), 18.2 (C_{14}), 18.0 (C_{11}), 13.1 (C_1), -1.2 (3 C, C_{16}). **HRMS(ESI):** calcd for $C_{14}H_{25}NNaO_2Si$ ($[M+Na]^+$): 290.1552; found: 290.1550;

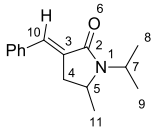
3-(Propan-2-ylidene)-1-((2-(trimethylsilyl)ethoxy)methyl)hexahydro-1H-indol-2(3H)-one 3.14n



Chemical Formula: $C_{17}H_{31}NO_2Si$
Exact Mass: 309,2124

Following general procedure **A**, 2-bromo-*N*-cyclohexyl-3-methyl-*N*-((2-(trimethylsilyl)ethoxy)methyl)but-2-enamide **3.13n** (100 mg, 0.27 mmol, 1.0 equiv) was reacted with cesium carbonate (134 mg, 0.41 mmol, 1.5 equiv), palladium allyl chloride (5.0 mg, 13 µmol, 5 mol%), PPh_3 (14.4 mg, 55 µmol, 20 mol%) and pivalic acid (8.3 mg, 83 µmol, 30 mol%) in mesitylene (2 mL) at 160°C overnight. The crude product was analyzed by GC/MC analysis showing complete conversion for dehalogenated by-product.

(*E*)-3-Benzylidene-1-isopropyl-5-methylpyrrolidin-2-one 3.14o



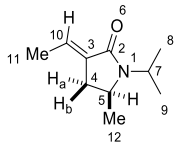
Chemical Formula: $C_{15}H_{19}NO$
Exact Mass: 229,1467

Following general procedure **A**, (*Z*)-2-bromo-*N*,*N*-diisopropyl-3-phenylacrylamide **3.13o** (100.0 mg, 0.32 mmol, 1.0 equiv) was reacted with cesium carbonate (157.5 mg, 0.48 mmol, 1.5 equiv), palladium allyl chloride (5.9 mg, 16 µmol, 5 mol%), PPh_3 (16.9 mg, 64 µmol, 20 mol%) and pivalic acid (9.9 mg, 96 µmol, 30 mol%) in mesitylene (2 mL) at 160°C overnight. The crude product was purified by preparative TLC (eluent: CyHex/EtOAc 90:10) affording (E)-3-Benzylidene-1-isopropyl-5-methylpyrrolidin-2-one **3.14o** (51.7 mg, 0.23 mmol, 70%) as a colorless oil.

The stereochemistry of the product was confirmed by NOE-spectroscopy.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.50 – 7.27 (m, 5H), 4.25 (sept, *J* = 6.9 Hz, 1H, H_7), 3.99 – 3.86 (m, 1H, H_5), 3.25 (ddd, *J* = 17.4, 8.1, 3.0 Hz, 1H, H_{4a}), 2.62 (dt, *J* = 17.4, 2.8 Hz, 1H, H_{4b}), 1.41 – 1.30 (m, 9H, H_8, H_9, H_{10}). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** δ = 168.8, 136.0, 131.5, 129.5, 129.0 (2 C), 128.6 (2 C), 128.2, 50.8, 45.1, 34.3, 23.6, 21.7, 19.4. **IR (neat):** ν = 2946, 1678 cm^{-1}. **HRMS(ESI)** calcd for $C_{15}H_{20}NO$ ($[M+H]^{+\cdot}$) : 230.1545; found: 230.1555;

(*E*)-3-Ethylidene-1-isopropyl-5-methylpyrrolidin-2-one 3.14q



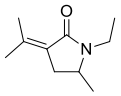
Chemical Formula: $C_{10}H_{17}NO$
Exact Mass: 167,1310

Following general procedure **A**, (2*Z*)-2-bromo-*N*,*N*-bis(propan-2-yl)but-2-enamide **3.13q** (100 mg, 0.40 mmol, 1 equiv) was reacted with cesium carbonate (196 mg, 0.60 mmol, 1.5 equiv) palladium allyl chloride (3.7 mg, 10 µmol, 2.5 mol%), PPh_3 (10.6 mg, 40 µmol, 10 mol%) and pivalic acid (12.3 mg, 0.12 mmol, 30 mol%) in mesitylene (2.8 mL) at 160°C overnight. The crude product was purified by flash chromatography (CyHex to 50% EtOAc) affording (E)-3-Ethylidene-1-isopropyl-5-methylpyrrolidin-2-one **3.14q** (52 mg, 0.31 mmol, 77 %) as a colorless oil.

The stereochemistry of the product was confirmed by NOE-spectroscopy.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.51 - 6.31 (m, 1 H, H_{10}), 4.11 (m, 1 H, H_7), 3.85 - 3.69 (m, 1 H, H_5), 2.85 - 2.69 (m, 1 H, H_{4a}), 2.21 - 2.09 (m, 1 H, H_{4b}), 1.76 - 1.65 (m, 3 H, H_{11}), 1.30 - 1.19 (m, 9 H, H_8, H_9, H_{12}). **^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz):** δ = 168.0, 132.6, 126.8, 50.4, 44.7, 31.6, 23.6, 21.7, 19.4, 14.5. **IR (neat):** ν = 2968, 2931, 1692, 1664, 1409, 720 cm^{-1}. **HRMS (ESI):** calcd for $C_{10}H_{18}NO$ ($[M+H]^+$): 168.1388; found: 168.1284;

1-ethyl-5-methyl-3-(propan-2-ylidene)pyrrolidin-2-one 3.14r



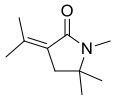
Chemical Formula: $C_{10}H_{17}NO$
Exact Mass: 167,1310

Following general procedure **A**, 2-bromo-*N*-ethyl-*N*-isopropyl-3-methylbut-2-enamide **3.13r** (50.0 mg, 0.20 mmol, 1.0 equiv) was reacted with cesium carbonate (98.5 mg, 0.30 mmol, 1.5 equiv), palladium allyl chloride (3.7 mg, 10 µmol, 5mol%), PPh_3 (10.6 mg, 40 µmol, 20 mol%) and pivalic acid (6.2 mg, 60 µmol, 30 mol%) in mesitylene (1 mL) at 160°C overnight. The

crude product was purified by preparative TLC (eluent: CyHex/EtOAc 90:10) affording 1-ethyl-5-methyl-3-(propan-2-ylidene)pyrrolidin-2-one **3.14r** (22.0 mg, 0.14 mmol, 67%) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.61 (spt, 1H), 3.24 (m, 2H), 2.75 (m, 2H), 2.31 (s, 3H), 1.85 (s, 3H), 1.27 (m, 6H) ppm. **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** δ = 166.1, 134.7, 109.1, 50.5, 46.6, 35.4, 22.8, 21.6, 20.6, 13.9 ppm. **IR (neat):** ν = 1637, 2934 cm^{-1}. **HRMS(ESI)** calcd (for $C_{10}H_{17}NO$) : 167.2111; found: 167.2123;

1,5,5-Trimethyl-3-(propan-2-ylidene)pyrrolidin-2-one 3.14s



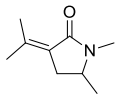
Chemical Formula: $C_{10}H_{17}NO$
Exact Mass: 167,1310

Following general procedure **A**, 2-bromo-*N*-(*tert*-butyl)-*N*,3-dimethylbut-2-enamide **3.13s** (100 mg, 0.4 mmol, 1.0 equiv) was reacted with cesium carbonate (197 mg, 0.60 mmol, 1.5 equiv), palladium allyl chloride (7.4 mg, 20 µmol, 5 mol%), PPh_3 (21.1 mg, 80 µmol, 20 mol%) and pivalic acid (12.4 mg, 120 µmol, 30 mol%) in mesitylene (2 mL) at 160°C overnight. The crude product was purified by flash chromatography (eluent: CyHex/EtOAc 90:10) affording 1,5,5-Trimethyl-3-(propan-2-ylidene)pyrrolidin-2-one **3.14s** (62 mg, 0.37 mmol, 92% yield) of a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.70 (s, 3H), 2.43 – 2.33 (m, 2H), 2.19 (t, J = 2.0 Hz, 3H), 1.67 (s, 3H), 1.14 (s, 6H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** δ = 168.4, 140.8, 123.7, 56.1, 40.8, 26.7, 24.0, 23.4, 19.1. **IR (neat):** ν = 2930, 1660, 1390, 1240 cm^{-1}. **HRMS(ESI):** calcd for $C_{10}H_{18}NO$ $([M+H]^+)$: 168.1386; found: 168.1383;

Following general procedure **A**, 2-bromo-*N*-isopropyl-*N*,3-dimethylbut-2-enamide (200 mg, 0.85 mmol, 1.0 equiv) was reacted with cesium carbonate (361 mg, 1.1 mmol, 1.5 equiv), palladium allyl chloride (15.6 mg, 42 µmol, 5 mol%), PPh_3 (45 mg, 170 µmol, 20 mol%) and pivalic acid (26 mg, 256 µmol, 30 mol%) in mesitylene (5.5 mL) at 160°C overnight. **GC/MS ratio 2s/4s/3s - 53:22:25** The crude product was purified by preparative thin layer chromatography (eluent CyHex/EA 9:1) affording (50 mg, 0.326 mmol, 38 %) of **3.14t** as a slightly yellow oil and **3.14t'** (15 mg, 0.098 mmol, 11 %) as a slightly yellow oil.

1,5-Dimethyl-3-(propan-2-ylidene)pyrrolidin-2-oneone 3.14t

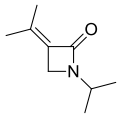


Chemical Formula: $C_9H_{15}NO$
Exact Mass: 153,1154

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.54 – 3.38 (m, 1H), 2.88 – 2.68 (m, 4H), 2.20 (s, 3H), 2.17 – 2.07 (m, 1H), 1.69 (s, 3H), 1.15 (d, J = 6.3 Hz, 3H).

^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz): δ = 169.1, 140.9, 123.7, 51.9, 33.2, 27.5, 23.5, 20.6, 18.9. **IR (neat):** ν = 2916, 1684, 1658, 1426, 1395, 1291 cm^{-1}. **HRMS(ESI):** calcd for $C_9H_{15}NNaO$ ($[M+Na]^{+\cdot}$): 176.1046; found: 176.1045;

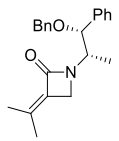
1-Isopropyl-3-(propan-2-ylidene)azetidin-2-one 3.14t'



Chemical Formula: $C_9H_{15}NO$
Exact Mass: 153,1154

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.01 (sept, J = 6.7 Hz, 1H), 3.60 (s, 2H), 2.02 (s, 3H), 1.68 (s, 3H), 1.18 (d, J = 6.7 Hz, 6H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** δ = 163.9, 134.0, 130.5, 43.6, 42.9, 20.9, 20.7, 19.8. **IR (neat):** ν = 2968, 1670, 1642, 1405, 1270 cm^{-1}. **HRMS(ESI):** calcd for $C_9H_{15}NNaO$ ($[M+Na]^{+\cdot}$): 176.1046; found: 176.1048;

1-((1*R*,2*S*)-1-(Benzyloxy)-1-phenylpropan-2-yl)-3-(propan-2-ylidene)azetidin-2-one 3.14u'

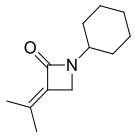


Chemical Formula: $C_{22}H_{25}NO_2$
Exact Mass: 335,1885

Following general procedure **A**, *N*-((1*R*,2*S*)-1-(benzyloxy)-1-phenylpropan-2-yl)-2-bromo-N,3-dimethylbut-2-enamide **3.13u** (200 mg, 0.48 mmol, 1 equiv) was reacted with cesium carbonate (235 mg, 0.72 mmol, 1.5 equiv) palladium allyl chloride (8.9 mg, 24 µmol, 2.5 mol%), PPh_3 (25 mg, 96 µmol, 10 mol%) and pivalic acid (15 mg, 0.14 mmol, 30 mol%) in mesitylene (3.1 mL) at 160°C overnight. The crude product was purified by flash chromatography (CyHex to 50% EtOAc) affording 1-((1R,2S)-1-(Benzyloxy)-1-phenylpropan-2-yl)-3-(propan-2-ylidene)azetidin-2-one **3.14u'** (75 mg, 0.22 mmol, 47 %) asa yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.41 – 7.27 (m, 10H), 4.61 (d, J = 5.0 Hz, 1H), 4.51 (d, J = 11.7 Hz, 1H), 4.31 (d, J = 11.7 Hz, 1H), 4.06 – 3.92 (m, 1H), 3.60 (d, J = 6.9 Hz, 1H), 3.48 (d, J = 6.9 Hz, 1H), 2.00 (s, 3H), 1.63 (s, 3H), 1.24 (d, J = 6.9 Hz, 3H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** δ = 164.0, 139.2, 138.4, 134.2, 130.9, 128.6, 128.5, 128.0, 127.7, 127.2, 83.6, 71.0, 53.0, 46.4, 20.9, 19.8, 12.7. **IR (neat):** ν = 2935, 2874, 1726, 1605, 1449, 1371, 1063 cm^{-1} **HRMS(ESI):** calcd for $C_{22}H_{26}NO2$ ($[M+H]^+$): 336.1958; found: 336.1950;

1-Cyclohexyl-3-(propan-2-ylidene)azetidin-2-one 3.14v

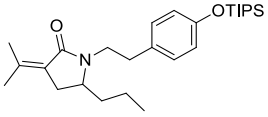


Chemical Formula: $C_{12}H_{19}NO$
Exact Mass: 193,1467

Following general procedure **A**, 2-bromo-*N*-cyclohexyl-*N*,3-dimethylbut-2-enamide **3.13v** (200 mg, 0.73 mmol, 1.0 equiv) was reacted with cesium carbonate (357 mg, 1.09 mmol, 1.5 equiv), palladium allyl chloride (13 mg, 36 µmol, 5 mol%), PPh_3 (38 mg, 145 µmol, 20 mol%) and pivalic acid (22 mg, 220 µmol, 30 mol%) in mesitylene (4.7 mL) at 160°C overnight. The crude product was purified by preparative thin layer chromatography (eluent CyHex/EA 9:1 to 1;1) affording 1-Cyclohexyl-3-(propan-2-ylidene)azetidin-2-one **3.14v'** (56 mg, 0.29 mmol, 40 %) of a slightly yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.65 – 3.53 (m, 3H), 2.00 (s, 3H), 1.89 – 1.78 (m, 2H), 1.78 – 1.69 (m, 2H), 1.66 (s, 3H), 1.64 – 1.55 (m, 1H), 1.40 – 1.22 (m, 4H), 1.19 – 1.02 (m, 1H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** δ = 163.9, 133.8, 130.6, 50.5, 44.3, 31.0, 25.5, 25.0, 20.9, 19.7. **IR (neat):** ν = 2935, 2856, 1716, 1390 cm^{-1} **HRMS(ESI):** calcd for $C_{12}H_{19}NNaO$ ($[M+Na]^{+\cdot}$): 216.1359; found: 216.1353;

3-(Propan-2-ylidene)-5-propyl-1-(4-((triisopropylsilyl)oxy)phenethyl)pyrrolidin-2-one 3.14w



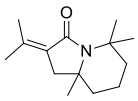
Chemical Formula: $C_{27}H_{45}NO_2Si$
Exact Mass: 443,3220

Following general procedure **A**, 2-bromo-3-methyl-*N*-(pentan-2-yl)-*N*-[2-(4-{[tris(propan-2-yl)silyl]oxy}phenyl)ethyl]but-2-enamide **3.13w** (5.93 g, 11.3 mmol, 1.0 equiv) was dissolved in mesitylene (75 mL) and was transferred to a Schlenk-flask containing Cs_2CO_3 (5.52 g, 16.95

mmol, 1.5 equiv), $[Pd(Cl)(C_3H_5)]_2$ (103 mg, 282 µmol, 2.5 mol%,), PPh_3 (296 mg, 1.13 mmol, 10 mol%) and PivOH (346 mg, 3.39 mmol, 30 mol%) and the reaction was heated using a preheated oil bath at 160°C for 15 h. The solution was cooled at room temperature, filtered over celite with EtOAc and concentrated. The crude product was purified by flash chromatography (CyHex/EtOAc 90:10) affording 3-(Propan-2-ylidene)-5-propyl-1-(4-((triisopropylsilyl)oxy)phenethyl)pyrrolidin-2-one **3.14w** (3.49 g, 7.86 mmol, 70%) as a yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.11 - 7.01 (m, 2 H), 6.84 - 6.75 (m, 2 H), 3.90 - 3.77 (m, 1 H), 3.38 - 3.23 (m, 1 H), 3.19 - 3.03 (m, 1 H), 2.91 - 2.77 (m, 1 H), 2.77 - 2.56 (m, 2 H), 2.30 - 2.14 (m, 4 H), 1.74 (s, 3 H), 1.34 - 1.14 (m, 7 H), 1.12 - 1.05 (m, 18 H), 0.91 (t, *J*=7.0 Hz, 3 H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** δ = 169.1, 154.6, 140.8, 131.8, 129.7, 124.0, 119.9, 54.1, 42.6, 36.1, 33.3, 30.9, 23.6, 19.0, 18.0, 18.0, 17.6, 14.2, 12.7. **IR (neat):** ν = 2942, 2866, 1682, 1661, 1508, 1261 cm^{-1}. **HRMS(ESI):** calcd for $C_{27}H_{46}NO_2Si$ ($[M+H]^+$): 444.3298; found: 444.3280;

5,5,8a-Trimethyl-2-(propan-2-ylidene)hexahydroindolizin-3(2*H*)-one 3.14x

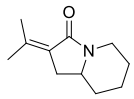


Chemical Formula: $C_{14}H_{23}NO$
Exact Mass: 221,1780

Following general procedure **A**, 2-bromo-3-methyl-1-(2,2,6,6-tetramethylpiperidin-1-yl)but-2-en-1-one **3.13x** (100 mg, 0.33 mmol, 1.0 equiv) was reacted with cesium carbonate (162 mg, 0.50 mmol, 1.5 equiv), palladium allyl chloride (6.1 mg, 17 µmol, 5 mol%), PPh_3 (17.4 mg, 66 µmol, 20 mol%) and pivalic acid (10.1 mg, 99 µmol, 30 mol%) in mesitylene (2 mL) at 160°C overnight. The crude product was purified by flash chromatography (eluent: CyHex/EtOAc 90:10) affording 5,5,8a-Trimethyl-2-(propan-2-ylidene)hexahydroindolizin-3(2H)-one **3.14x** (61 mg, 0.28 mmol, 83% yield) as a colorless oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.43 – 2.39 (m, 2H), 2.18 (s, 3H), 1.76 (s, 3H), 1.70 – 1.50 (m, 6H), 1.40 (s, 3H), 1.37 (s, 3H), 1.16 (s, 3H). **^{13}C NMR ($CDCl_3$, 75 MHz):** δ = 169.1, 140.5, 124.8, 57.4, 53.6, 44.3, 39.8, 37.3, 30.1, 27.7, 25.9, 23.6, 19.0, 17.0. **IR (neat):** ν = 2930, 1651, 1609 cm^{-1}. **HRMS(ESI):** calcd for $C_{14}H_{24}NO$ ($[M+H]^+$) : 222.1852; found: 222.1858;

2-(Propan-2-ylidene)hexahydroindolizin-3(2*H*)-one 3.14y

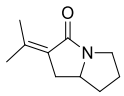


Chemical Formula: $C_{11}H_{17}NO$
Exact Mass: 179,1310

Following general procedure **A**, 2-bromo-3-methyl-1-(2-methylpiperidin-1-yl)but-2-en-1-one **3.13y** (2.3 g, 8.84 mmol, 1 equiv) was reacted with cesium carbonate (4.3 g, 13.3 mmol, 1.5 equiv), palladium allyl chloride (160 mg, 0.44 mmol, 5 mol%,), PPh_3 (463 mg, 1.77 mmol, 20 mol%) and PivOH (270 mg, 2.65 mmol, 30 mol%) in mesitylene (57 mL) at 160°C overnight. The crude product was purified by flash chromatography (CyHex to 20% EtOAc) affording 2-(Propan-2-ylidene)hexahydroindolizin-3(2H)-one **3.14y** (1.109 g, 6.18 mmol, 70 %) as a yellow solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.23 - 4.12 (m, 1 H), 3.35 (dddd, *J*=11.3, 8.1, 4.9, 3.2 Hz, 1 H), 2.86 - 2.74 (m, 1 H), 2.62 (td, *J*=12.7, 3.5 Hz, 1 H), 2.28 - 2.23 (m, 3 H), 2.22 - 2.11 (m, 1 H), 1.90 - 1.79 (m, 2 H), 1.770 - 1.70 (m, 3 H), 1.70 - 1.62 (m, 1 H), 1.50 - 1.26 (m, 2 H), 1.18 - 1.05 (m, 1 H).**^{13}C{^{1}H} NMR ($CDCl_3$, 101 MHz):** δ = 167.7, 141.0, 123.9, 53.8, 40.1, 34.1, 32.0, 24.8, 24.1, 23.7, 19.0. **IR (neat):** ν = 2934, 2851, 1680, 1658, 1421, 1298 cm^{-1}. **Mp** = 41-42 °C. . **HRMS(ESI):** calcd for $C_{11}H_{17}NNaO$ ($[M+Na]^+$): 202.1205; found: 202.1202;

2-(Propan-2-ylidene)tetrahydro-1H-pyrrolizin-3(2H)-one 3.14z

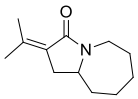


Chemical Formula: $C_{10}H_{15}NO$
Exact Mass: 165,1154

Following general procedure **A**, 2-bromo-3-methyl-1-(2-methylpyrrolidin-1-yl)but-2-en-1-one **3.13z** (200 mg, 0.81 mmol, 1 equiv) was reacted with cesium carbonate (397 mg, 1.2 mmol, 1.5 equiv), palladium allyl chloride (15 mg, 41 µmol, 5 mol%,), PPh_3 (42 mg, 160 µmol, 20 mol%) and PivOH (25 mg, 240 µmol, 30 mol%) in mesitylene (5.3 mL) at 160°C overnight. The crude product was purified by flash chromatography (CyHex to 40% EtOAc) affording 2-(Propan-2-ylidene)tetrahydro-1H-pyrrolizin-3(2H)-one **3.14z** (30 mg, 0.18 mmol, 22 %) asa yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.72 – 3.65 (m, 1H), 3.65 – 3.59 (m, 1H), 3.16 – 3.05 (m, 1H), 2.87 (m, 1H), 2.45 – 2.32 (m, 1H), 2.21 (m, 3H), 2.06 – 1.84 (m, 3H), 1.73 (s, 3H), 1.31 – 1.11 (m, 2H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** δ = 170.5, 141.6, 127.1, 57.6, 42.1, 32.8, 31.6, 26.0, 23.5, 19.1. **IR (neat):** ν = 2917, 2842, 1675, 1421, 1298 cm^{-1}. **HRMS(ESI):** calcd for $C_{10}H_{15}NNaO$ ($[M+Na]^{+\cdot}$): 188.1051; found: 188.1058;

2-(Propan-2-ylidene)hexahydro-1H-pyrrolo[1,2-a]azepin-3(2H)-one 3.14aa



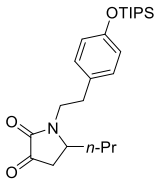
Chemical Formula: $C_{12}H_{19}NO$
Exact Mass: 193,1467

Following general procedure **A**, 2-bromo-3-methyl-1-(2-methylazepan-1-yl)but-2-en-1-one **3.13aa** (200 mg, 0.73 mmol, 1 equiv) was reacted with cesium carbonate (356 mg, 1.09 mmol, 1.5 equiv), palladium allyl chloride (13.3 mg, 36 µmol, 5 mol%,), PPh_3 (38 mg, 145 µmol, 20 mol%) and PivOH (22 mg, 220 µmol, 30 mol%) in mesitylene (4.7 mL) at 160°C overnight. The crude product was purified by flash chromatography (CyHex to 40% EtOAc) affording 2-(Propan-2-ylidene)hexahydro-1H-pyrrolo[1,2-a]azepin-3(2H)-one **3.14aa** (84 mg, 0.43 mmol, 60 %) of a yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.76 – 3.65 (m, 1H), 3.65 – 3.54 (m, 1H), 2.98 (m, 1H), 2.71 (m, 1H), 2.16 (m, 3H), 2.15 – 2.05 (m, 1H), 1.89 – 1.69 (m, 2H), 1.67 (s, 3H), 1.63 – 1.40 (m, 6H). **^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz):** δ = 169.0, 139.7, 124.5, 55.3, 42.7, 36.6, 33.0, 29.5, 27.3, 25.0, 23.3, 18.8. **IR (neat):** ν = 2925, 2857, 1683, 1659, 1443, 1414, 1297 cm^{-1}. **HRMS(ESI):** calcd for $C_{12}H_{20}NNaO$ ($[M+Na]^{+\cdot}$): 216.1359; found: 216.1355;

3.4. Attempts toward a total synthesis of plakoridine A

5-propyl-1-(4-((triisopropylsilyl)oxy)phenethyl)pyrrolidine-2,3-dione 3.43

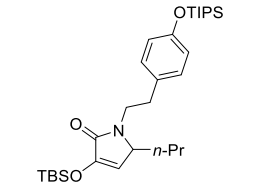


Chemical Formula: $C_{24}H_{39}NO_3Si$
Exact Mass: 417.2699

To a solution of **3.14w** (1.564 g, 3.53 mmol, 1 equiv) in DCM was bubbled ozone at -78 °C until the solution was saturated in ozone. A flux of argon was used to removed excess of ozone and DMS (1.49 mL, 20.2 mmol, 5.7 equiv) is added dropwise at -78°C. The reaction was stirred during 30 min at -78°C, then the solution was allowed to warm up temperature. The crude mixture was evaporated under vacuo, diluted with DCM and water, extracted with DCM. The combined organic layers were dried over $MgSO_4$ and evaparated under reduce pressure to afford the title compound (1.4 g, 3.35 mmol, 95%) without further purification (unstable on silica gel).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.00 – 6.96 (m, 2H), 6.76 – 6.72 (m, 2H), 4.07 – 3.91 (m, 1H), 3.52 – 3.42 (m, 1H), 3.26 (dt, J = 14.1, 7.6 Hz, 1H), 2.96 – 2.84 (m, 1H), 2.81 – 2.71 (m, 1H), 2.56 (dd, J = 19.7, 7.2 Hz, 1H), 2.23 (dd, J = 19.7, 2.5 Hz, 1H), 1.77 – 1.62 (m, 1H), 1.19 – 1.12 (m, 6H), 1.02 – 0.97 (m, 18H), 0.85 (t, J = 7.2 Hz, 3H). **$^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz):** δ = 198.7, 159.9, 154.9, 130.4, 129.5, 120.1, 52.3, 43.8, 37.3, 35.4, 32.4, 17.9, 17.4, 13.8, 12.6.

3-((tert-butyldimethylsilyl)oxy)-5-propyl-1-(4-((triisopropylsilyl)oxy)phenethyl)-1,5-dihydro-2H-pyrrol-2-one 3.52



Chemical Formula: $C_{30}H_{53}NO_3Si_2$
Exact Mass: 531.3564

To a solution of **3.43** (45 mg, 0.11 mmol, 1 equiv) and 2,6-lutidine (15 mL, 0.13 mmol, 1.2 equiv) in dichloromethane (0.5 mL) at -78°C was added dropwise TBSOTf (27.3 mL, 0.12 mmol, 1.1 equiv). The reaction mixture was stirred at -78°C during 10 minutes and allowed to reach room temperature. Then, the reaction mixture was quench with a saturated solution of $NaHCO_3$, extracted with DCM. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduce pressure. The crude mixture was puridifed by silica gel chromatography to afford the desired product as a yellow oil (30 mg, 0.056 mmol, 52%).

^{1}H NMR ($CDCl_3$, 300 MHz): 7.06 – 6.99 (m, 2H), 6.85 – 6.76 (m, 2H), 5.74 (d, J = 2.2 Hz, 1H), 3.95 (ddd, J = 14.1, 8.3, 5.8 Hz, 1H), 3.67 – 3.57 (m, 1H), 3.16 (dt, J = 14.3, 7.6 Hz, 1H), 2.91 – 2.71 (m, 2H), 1.71 – 1.58 (m, 1H), 1.28 – 1.14 (m, 6H), 1.14 – 1.03 (m, 18H), 0.96 (s, 9H), 0.89 (t, J = 7.2 Hz, 3H), 0.23 (s, 6H). **$^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz):** δ =167.3, 154.7, 147.4, 131.5, 129.7, 120.1, 117.3, 56.6, 42.1, 34.1, 33.1, 25.8, 18.5, 18.1, 17.4, 14.3, 12.8, -4.5.

3.5. Total synthesis of (±)-δ-Coniceine

Chemical Formula: $C_8H_{16}ClN$
Exact Mass: 161,0971

A solution of 2-(propan-2-ylidene)hexahydroindolizin-3(2H)-one **3.14y** (208 mg, 1.16 mmol, 1 equiv) in DCM (12 mL) was cooled down to -78°C and ozone was bubbled in the mixture solution until apparation of persistent blue coloration. Then, oxygene was bubbled to eliminate

excess of ozone and $NaBH_4$ (131 mg, 3.48 mmol, 3 equiv) was added in one portion. The mixture was stirred 30 min at -78°C and then allowed to room temperature. Spatula of silica was added and the crude product was filtered on a pad of silica (CyHex to 100 % EtOAc) affording 150 mg of diastereoisomers **3.55** (0.962 mmol, 83 %) as a yellow oil. The product is enough pure to engage it directly in the next step. The crude alcohol (150 mg, 0.962 mmol, 1 equiv) in dry dichloromethane (2 mL) under an argon atmosphere was treated with a solution of carbon tetrabromide (1.6 g, 4.8 mmol, 5 equiv) in dry dichloromethane (1.5 mL) followed by triphenylphosphine (1.26 g, 4.8 mmol, 5 equiv). The reaction mixture was stirred for 24 h, poured into saturated aqueous sodium hydrogencarbonate and extracted with dichloromethane. The combined organic extracts were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was triturated with ethyl acetate and the organic solution was filtered and evaporated under reduced pressure. The residue was purified by flash chromatography on silica (CyHex to 50 % EtOAc) affording 209 mg of diastereoisomers (0.962 mmol, 99 %) as a yellow oil. Solution of the bromide (209 mg, 0.962 mmol, 1 equiv) in toluene (27 mL) was treated with tributyltin hydride (0.78 mL, 2.9 mmol, 3 equiv) and AIBN (16 mg, 0.096 mmol, 0.1 equiv), and the reaction mixture was heated at reflux under an argon atmosphere for 2 h. The reaction mixture was poured into saturated aqueous sodium hydrogen carbonate and extracted three times with ethyl acetate. The combined organic extracts were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography on silica (CyHex to 50 % EtOAc) affording 123 mg of the lactam **3.56** (0.88 mmol, 92%) as a slightly yellow oil. The physical data were in accordance to the litterature[186]. To a suspension of lithium aluminium hydride (65.5 mg, 1.72 mmol, 2 equiv) in anhydrous tetrahydrofuran (8 mL), under a nitrogen atmosphere at 0°C, a solution of lactam (123 mg, 0.88 mmol, 1 equiv) in anhydrous tetrahydrofuran (7 mL) was added slowly. The resulting mixture was stirred at room temperature for 2 hours. After hydrolysis with saturated aqueous ammonium chloride (10 mL), ethyl acetate (15 mL) was added and the mixture was stirred during 30 minutes. The organic phase was separated, dried over $MgSO_4$, and HCl gas was bubbled in the organic phase during 15 minutes. The crude product was purified by flash chromatography (EtOAc/MeOH 100:0 to 90:10) affording 125 mg (0.77 mmol, 90 %) of a white solid.

^{1}H NMR (DMSO-*d*$_6$, 300 MHz): δ = 2.88 – 2.72 (m, 2H), 2.35 – 2.17 (m, 2H), 2.16 – 2.05 (m, 1H), 1.53 – 1.42 (m, 1H), 1.42 – 1.34 (m, 1H), 1.33 – 1.25 (m, 1H), 1.25 – 1.10 (m, 3H), 1.04 – 0.79 (m, 3H), 0.79 – 0.66 (m, 2H). **^{13}C{^{1}H} NMR (DMSO-*d*$_6$, 101**

MHz): δ = 58.4, 45.6, 44.6, 20.3, 19.6, 14.6, 14.3, 11.5. **IR (neat):** ν = 2930, 1650, 1555 cm^{-1}. **HRMS(ESI):** calcd for $C_8H_{16}N$ ($[M+H]^{+\cdot}$): 126.1277; found: 126.1282;

3.6. General procedure

Amines's synthesis

Method A

Amines (2 equiv), aldehyde (1 equiv) and 4Å molecular sieves were stirred for 4h in THF (0.1M). Then, a solution of $NaBH_4$ (2 equiv) in EtOH (0.1 M) was carefully added to the mixture. The reaction was stirred at room temperature overnight, and was then filtered through celite. The crude was then acidified using a solution of HCl (0.1M) and stirred for 30 minutes. The mixture was then basified using NaOH solution (0.1M) and extracted three times using AcOEt. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The excess of starting material was removed under high vacuum to provide the amine. The amines were used without purification, or were purified by chromatography on silica gel using DCM/MeOH as eluent.

Method B

Amines (1 equiv), aldehyde (1 equiv), and AcOH (2 equiv) were stirred at room temperature in DCE (0.1 M) for 30 minutes. $NaBH(OAc)_3$ (2 equiv) was then added to the turning solution, which was reacted overnight. Then, the mixture was quenched using a solution of NaOH (1M) and the crude was stirred for further 30 minutes. The crude was extracted twice with DCM, dried over sodium sulfate, filtered and evaporated under vacuum to give the desired amines. The amines were used without purification, or were purified by chromatography on silica gel using DCM/MeOH as eluent.

Method C

Amine (1 equiv), ketone/aldehyde (1 equiv) were dissolved in MeOH (0.7M) and purged with argon. Pd/C (10 mol%) was carefully added and the flask was purged with H_2. The mixture was stirred overnight under H_2 balloon. The crude was then filtered through celite, and the solvent evaporated. The resulting amines were used without further purification or were purified by chromatography on silica gel using DCM/MeOH as eluent.

Phosphine's synthesis

TADDOL

In a two-neck-flask equipped with magnetic stirring bar and reflux condenser were placed active magnesium turning (53 mmol, 5.3 equiv) and suspended in THF (30 mL). To this suspension a solution of the arylhalide (50 mmol, 5.0 equiv) in THF (10 mL) was added. If the exothermic reaction did not start after 5 minutes, iodine was added and the reaction mixture warmed by a oil bath. After the start of the exothermic reaction, the reaction mixture was refluxed for 30 minutes and afterwards cooled down to room temperature. A solution of dicarboxylate (10 mmol, 1.0 equiv) in THF or ether (40 mL) was added slowly, keeping the internal temperature below the boiling point of the solvent. After complete addition, the reaction mixture was refluxed for 8-14 h and afterwards cooled down to room temperature. Saturated ammonium chloride solution (40 mL), hydrochloric acid (1.0 M, 10 mL) and water (50 mL) were added carefully. The resulting biphasic mixture was extracted with ether (4x 50 mL). The combined organic extracts were washed with brine (30 mL) and dried over sodium sulfate. All volatiles were removed under reduced pressure. The crude product was purified by column chromatography (SiO_2, Pentane: Et_2O).

Dichloroarylphosphine

To a solution of chlorobis(diethylamino)phosphine (1.1 equiv) in dry Et_2O (1 mL/mmol) at -78°C was added a freshly prepared solution of a Grignard or an organolithium reagent (1.0 to 1.5 equiv, 0.5 to 2 M in Et_2O) slowly *via* a cannula. After complete addition, the reaction mixture was allowed to warm up to rt and stirred for an additional hour. In case an organolithium reagent was used the reaction, mixture was used as such for the next step. When Grignard reagent were used, the reaction mixture was filtered using a Schlenk-frit and the residue was washed with additional Et_2O (~0.5 mL/mmol). The filtrate was concentrated with a rotary evaporator under N_2-atmosphere and the obtained oil was redissolved in Et_2O (~0.5 mL/mmol). The reaction mixture was cooled to 0 °C and a solution of hydrogenchloride (4.4 to 5 equiv equiv, 2M in Et_2O) was added dropwise. After complete addition, the reaction mixture was allowed to warmup to rt and stirred for an additional hour. The white precipitate formed was filtered off (Schlenk-frit). The residue was washed with additional Et_2O (~0.5 mL/mmol) and the filtrate was concentrated with a rotary evaporator under N_2-atmosphere. The crude product was purified by distillation under high vacuum.

Phosphine

To a mixture of TADDOL of (0.3 mmol, 1 equiv) and 4Å molecular sieves (75 mg) in THF (1.2 mL) at 0°C was added triethylamine (0.70 mmol, 2.34 equiv). Next, dichloroarylphosphine (0.33 mmol, 1.1 equiv) was added dropwise. The reaction was allowed to warm to room temperature and stirred for 2 h. The reaction was diluted with Et_2O, filtered through celite, and concentrated under reduced pressure. Column chromatography (SiO_2, Pentane: Et_2O) afforded phosphonite ligand as a white solid.

Carbamoyl chloride's synthesis

The carbamoyl chloride was not submitted to heating. The carbamoyl chloride was freshly used and stocked in a freezer (-30 °C). The yield of the reaction didn't show any loss of efficiency after sotcking in freezer for severals days.

Amines (1 equiv) dissolved in dry benzene (0.4M) and Et_3N (1.2 equiv) were slowly added to a stirred solution of triphosgene (0.34 equiv) in dry benzene (0.4M) at 0 °C. The mixture was then slowly allowed to reach room temperature and was stirred overnight. The crude was then quenched with HCl solution (1M) and extracted twice with DCM. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The excess of benzene was removed by coevaporation with $CHCl_3$. The desired carbamoyl chloride was used without further purification.

Palladium-catalyzed C(sp^3)-H activation

Conditions A: Double-chamber system:

General scale synthesis:

Chamber A: CO generator:

Chamber A, equipped with a stirring bar, was filled in a glovebox with $Pd(OAc)_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(*t*-Bu)$_3$●HBF_4 (12 mg, 0.04 mmol, 30 mol%), and COgen (97 mg, 0.4 mmol, 3.0 equiv).

Chamber B: Substrate chamber:

Chamber B, previously charged with substrate (0.133 mmol, 1 equiv) and stirring bar, was added $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv).

Both chambers were sealed with screwcap, and removed from the glovebox. Mesitylene (2.62 mL) was added to chamber B, followed by addition of Cy_2NMe (161 mg, 0.798 mmol, 6.0 equiv) in 0.5 mL of mesitylene in chamber A. The COware system was heated at 120 °C in an oil bath and stirred for 18h. The excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent.

Conditions A: Double-chamber system:

Tenfold scale synthesis:

Chamber A: CO generator:

Chamber A, equipped with a stirring bar, was filled in a glovebox with $Pd(OAc)_2$ (89 mg, 0.4 mmol, 30 mol%), $P(t\text{-}Bu)_3 \bullet HBF_4$ (120 mg, 0.4 mmol, 30 mol%), and COgen (970 mg, 4 mmol, 3.0 equiv).

Chamber B: Substrate chamber:

Chamber B, previously charged with substrate (1.33 mmol, 1 equiv) and stirring bar, was added $PdCl_2$ (24 mg, 0.133 mmol, 10 mol%), cataCXium AHI (120 mg, 0.266 mmol, 20 mol%), pivalic acid (41 mg, 0.4 mmol, 30 mol%) and cesium carbonate (1.3 g, 4 mmol, 3.0 equiv).

Both chambers were sealed with screwcap, and removed from the glovebox. Mesitylene (26.2 mL) was added to chamber B, followed by addition of Cy_2NMe (161 mg, 0.798 mmol, 6.0 equiv) in 5 mL of mesitylene in chamber A. The double chamber system was heated at 120 °C in an oil bath and stirred for 18h. The excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent.

Conditions B: CO atmosphere

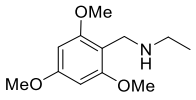
Standard scale synthesis:

In a glovebox, a 10-mL vial, charged with carbamoyl chloride substrates (0.133 mmol) and stirring bar, was filled with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv). The vial was sealed, removed from the glovebox and purged with CO balloon. Mesitylene (2.62 mL) was added and the mixture placed in a preheated block at 120 °C. The solution was stirred for 18h, and the excess of mesitylene was removed by

flushing cyclohexane on silica gel. The resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent.

3.7. Amine's synthesis

<u>*N*-(2,4,6-trimethoxybenzyl)ethanamine 4.13b</u>

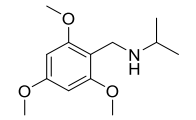


Chemical Formula: $C_{12}H_{19}NO_3$
Exact Mass: 225.1365

Following general procedure **A**, ethylamine (70 % in MeOH, 25.5 mmol, 5 equiv), 2,4,6-trimethoxybenzaldehyde (1 g, 5.1 mmol,1 equiv), were reacted in THF (10 mL) for 4h with 4Å molecular sieves (2.5 g, 6.5 mmol.). $NaBH_4$ (580 mg, 15.3 mmol, 3 equiv) in EtOH (6 mL) was carefully added and the mixture was stirred overnight. The crude was purified by chromatography on silica gel using DCM/MeOH as eluent to provide *N*-(2,4,6-trimethoxybenzyl)ethanamine **4.13b** as a yellowish oil (1.1 g, 4.90 mmol, 96 %).

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 6.11 (s, 2H), 3.79 (s, 3H), 3.78 (s, 6H), 3.76 (s, 2H), 2.59 (q, *J* = 7.2 Hz, 2H), 1.65 (br. s, 1H), 1.08 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR ($CDCl_3$, 101 MHz) :** δ = 160.3, 159.4, 109.5, 90.4, 55.7, 55.4, 43.2, 41.2, 15.5. **IR (neat):** ν = 2953, 1581, 1473 cm^{-1}. **HRMS (ESI):** Calculated for $C_{12}H_{20}NO_3$ ($[M+H]^+$): 226.1438; found: 226.1440

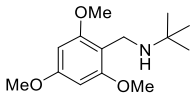
<u>*N*-(2,4,6-trimethoxybenzyl)propan-2-amine 4.13a</u>



Chemical Formula: $C_{13}H_{21}NO_3$
Exact Mass: 239.1521

N-(2,4,6-trimethoxybenzyl)propan-2-amine was obtained according to a known procedure[187].

<u>2-methyl-*N*-(2,4,6-trimethoxybenzyl)propan-2-amine 4.13c</u>



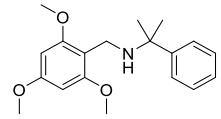
Chemical Formula: $C_{14}H_{23}NO_3$
Exact Mass: 253.1678

Following general procedure **B**, 2,4,6-trimethoxybenzaldehyde (1 g, 5.1 mmol, 1 equiv), tertbutylamine (0.541 mL, 5.1 mmol, 1 equiv), AcOH (0.583 mL, 10.2 mmol, 2 equiv) and. $NaBH(OAc)_3$ (2.16 g, 10.2 mmol, 2 equiv) were reacted in DCE (25 mL) overnight.

The crude mixture was purified by chromatography on silica gel using DCM/MeOH as eluent, yielding 2-methyl-N-(2,4,6-trimethoxybenzyl)propan-2-amine **4.13c** (1.25 g, 5.0 mmol, 97 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.10 (s, 2H), 3.79 (s, 6H), 3.78 (s, 3H), 3.70 (s, 2H), 1.43 (br.ns, 1H), 1.16 (s, 9H). **^{13}C NMR ($CDCl_3$, 101 MHz) :** δ = 160.2, 159.2, 110.3, 90.7, 55.7, 55.4, 50.6, 35.1, 29.2. **IR (neat):** ν = 2960, 1598, 1463, 1205 cm^{-1}. **HRMS (ESI):** Calculated for $C_{14}H_{24}NO_3$ ($[M+H]^+$): 254.1751; found: 254.1753

2-phenyl-*N*-(2,4,6-trimethoxybenzyl)propan-2-amine 4.13d

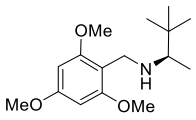


Chemical Formula: $C_{19}H_{25}NO_3$
Exact Mass: 315.1834

Following general procedure **B**, 2,4,6-trimethoxybenzaldehyde (700 mg, 3.57 mmol, 1 equiv), cumylamine (483 mg, 3.57 mmol, 1 equiv), AcOH (0.408 mL, 7.14 mmol, 2 equiv) and. $NaBH(OAc)_3$ (1.51 g, 7.14 mmol, 2 equiv) were reacted in DCE (15 mL) overnight. The crude was purified by chromatography on silica gel using DCM/MeOH as eluent, yielding 2-phenyl-N-(2,4,6-trimethoxybenzyl)propan-2-amine **4.13d** (1.02 g, 3.2 mmol, 90 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.57 – 7.47 (m, 2H), 7.33 (dd, *J* = 8.5, 7.0 Hz, 2H), 7.24 – 7.17 (m, 1H), 6.07 (s, 2H), 3.75 (s, 3H), 3.75 (s, 6H), 3.45 (s, 2H), 1.52 (s, 6H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 160.2, 159.1, 148.0, 127.8, 126.1, 125.9, 109.8, 90.6, 55.9, 55.6, 55.3, 35.5, 29.8. **IR (neat):** ν = 2961, 1596, 1460, 1127 cm^{-1}. **HRMS (ESI):** Calculated for $C_{19}H_{26}NO_3$ ($[M+H]^+$): 316.1913; found: 316.1917

(*R*)-3,3-*d*imethyl-*N*-(2,4,6-trimethoxybenzyl)butan-2-amine 4.13e

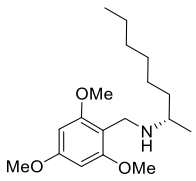


Chemical Formula: $C_{16}H_{27}NO_3$
Exact Mass: 281.1991

Following general procedure **B**, 2,4,6-trimethoxybenzaldehyde (1 g, 5.1 mmol, 1 equiv), (*R*)-3,3-dimethylbutan-2-amine (0.7 mL, 5.1 mmol, 1 equiv), AcOH (0.583 mL, 10.2 mmol, 2 equiv) and. $NaBH(OAc)_3$ (2.16 g, 10.2 mmol, 2 equiv) were reacted in DCE (25 mL) overnight. The crude mixture was purified by chromatography on silica gel using DCM/MeOH as eluent, yielding (*R*)-3,3-*d*imethyl-*N*-(2,4,6-trimethoxybenzyl)butan-2-amine **4.13e** (1.4 g, 5.0 mmol, 98 %).

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 6.11 (s, 2H), 3.88 – 3.71 (m, 11H), 2.09 (q, *J* = 6.4 Hz, 1H), 1.83 (br. s, 1H), 0.97 (d, *J* = 6.3 Hz, 3H), 0.81 (s, 9H). **^{13}C NMR ($CDCl_3$, 101 MHz) :** δ = 160.1, 159.6, 109.6, 90.5, 60.4, 55.7, 55.4, 40.1, 34.1, 26.6, 14.8. **IR (neat):** ν = 2954, 1607, 1140, 1204 cm^{-1}. **HRMS (ESI):** Calculated for $C_{16}H_{28}NO_3$ ($[M+H]^+$): 282.2064; found: 282.2062

(*S*)-*N*-(2,4,6-trimethoxybenzyl)octan-2-amine 4.13f

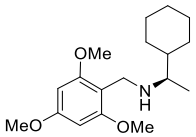


Chemical Formula: $C_{18}H_{31}NO_3$
Exact Mass: 309.2304

Following general procedure **B**, 2,4,6-trimethoxybenzaldehyde (1.38 g, 7.03 mmol, 1 equiv), (*S*)-octan-2-amine (1 g, 7.03 mmol, 1 equiv), AcOH (0.804 mL, 14.06 mmol, 2 equiv) and. $NaBH(OAc)_3$ (2.98 g, 14.06 mmol, 2 equiv) were reacted in DCE (14 mL) overnight. The crude mixture was purified by chromatography on silica gel using DCM/MeOH as eluent, yielding (*S*)-*N*-(2,4,6-trimethoxybenzyl)octan-2-amine **4.13f** (1.8 g, 5.8 mmol, 83 %).

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 6.08 (s, 2H), 3.84 – 3.72 (m, 11H), 2.71 – 2.62 (m, 1H), 2.55 – 2.46 (m, 1H), 1.52 – 1.38 (m, 1H), 1.32 – 1.17 (m, 10H), 1.04 (d, *J* = 6.3 Hz, 3H), 0.84 (t, *J* = 6.6 Hz, 3H). **^{13}C NMR ($CDCl_3$, 101 MHz) :** δ = 160.3, 159.4, 108.8, 90.4, 55.6, 55.3, 51.7, 38.7, 36.8, 32.0, 29.5, 26.0, 22.7, 20.2, 14.2. **IR (neat):** ν = 2933, 2820, 1623, 1156 cm^{-1}. **HRMS (ESI):** Calculated for $C_{18}H_{32}NO_3$ ($[M+H]^+$): 310.2382; found: 310.2387

(*R*)-1-cyclohexyl-*N*-(2,4,6-trimethoxybenzyl)ethan-1-amine 4.13g

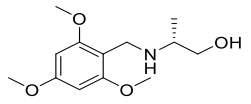


Chemical Formula: $C_{18}H_{29}NO_3$
Exact Mass: 307.2147

Following general procedure **B**, 2,4,6-trimethoxybenzaldehyde (1.38 g, 7.03 mmol, 1 equiv), *R*-(-)-Cyclohexylethylamine (0.95 mL, 7.03 mmol, 1 equiv), AcOH (0.804 mL, 14.06 mmol, 2 equiv) and. $NaBH(OAc)_3$ (2.98 g, 14.06 mmol, 2 equiv) were reacted in DCE (14 mL) overnight. The crude mixture was purified by chromatography on silica gel using DCM/MeOH as eluent, yielding (*R*)-1-cyclohexyl-*N*-(2,4,6-trimethoxybenzyl)ethan-1-amine **4.13g** (1.95 g, 6.33 mmol, 90 %).

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 6.11 (s, 2H), 3.83 – 3.72 (m, 11H), 2.37 – 2.29 (m, 1H), 1.76 – 1.61 (m, 5H), 1.40 – 1.29 (m, 1H), 1.27 – 1.07 (m, 3H), 1.00 (d, *J* = 6.4 Hz, 3H), 0.97 – 0.84 (m, 2H). **^{13}C NMR ($CDCl_3$, 101 MHz) :** δ = 160.3, 159.5, 90.5, 56.5, 55.8, 55.4, 42.7, 39.1, 29.9, 28.3, 26.9, 26.8, 26.7, 16.7. **IR (neat):** ν = 2923, 2850, 1603, 1149 cm^{-1}. **HRMS (ESI):** Calculated for $C_{18}H_{30}NO_3$ ($[M+H]^+$): 308.2220; found: 308.2222

(*R*)-2-((2,4,6-trimethoxybenzyl)amino)propan-1-ol

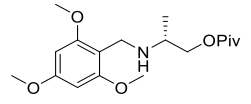


Chemical Formula: $C_{13}H_{21}NO_4$
Exact Mass: 255.1471

Following general procedure **C**, 2,4,6-trimethoxybenzaldehyde (1.5 g, 7.63 mmol, 1 equiv), *L*-alanilol (573 mg, 7.63 mmol, 1 equiv) and Pd/C (812 mg, 10% w/w, 10 mol%) were reacted in MeOH (11 mL) and stirred overnight under H_2 atmosphere. The crude mixture was purified by chromatography on silica gel to provide (*R*)-2-((2,4,6-trimethoxybenzyl)amino)propan-1-ol (686 mg, 2.67 mmol, 35 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.10 (s, 2H), 3.81 (d, *J* = 12.5 Hz, 1H + NH), 3.78 – 3.77 (m, 9H), 3.73 (d, *J* = 12.6 Hz, 1H), 3.59 (dd, *J* = 10.7, 4.0 Hz, 1H), 3.24 (dd, *J* = 10.7, 6.3 Hz, 1H), 2.70 (td, *J* = 6.4, 4.0 Hz, 1H + OH), 1.02 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$) δ** = 160.4, 159.4, 108.9, 90.5, 65.1, 55.7, 55.4, 53.0, 38.5, 17.4. **IR (neat):** ν = 3132, 2925, 2840, 1608, 1139 cm^{-1}. **HRMS (ESI):** Calculated for $C_{13}H_{22}NO_4$ ($[M+H]^+$): 256.1543; found: 256.1544

(*R*)-2-((2,4,6-trimethoxybenzyl)amino)propyl pivalate 4.13h



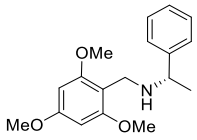
Chemical Formula: $C_{18}H_{29}NO_5$
Exact Mass: 339.2046

(*R*)-2-((2,4,6-trimethoxybenzyl)amino)propan-1-ol (300 mg, 1.18 mmol, 1 equiv) was dissolved in dichloromethane (6 mL) and cooled to 0 °C. Triethylamine (0.201 mL, 1.43 mmol, 1.2 equiv) and DMAP (7.2 mg, 0.06 mmol, 5 mol%) were added, followed by drop-wise addition of pivaloyl chloride (0.163 mL, 1.3 mmol, 1.1 equiv). The reaction mixture was allowed to warm slowly to ambient temperature and stirred for 16 h. The reaction mixture was quenched with water (10 mL) and extracted with dichloromethane (2 x 10 mL).

The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. The residue was purified by chromatography on silica gel using DCM/MeOH as eluent to afford (*R*)-2-((2,4,6-trimethoxybenzyl)amino)propyl pivalate **4.13h** as yellowish oil (200 mg, 0.58 mmol, 50 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.11 (s, 2H), 4.05 – 4.00 (m, 1H), 3.92 – 3.86 (m, 1H), 3.82 (d, *J* = 5.5 Hz, 2H), 3.80 (s, 3H), 3.78 (s, 6H), 3.33 (br. s, 1H), 2.90 – 2.80 (m, 1H), 1.17 (s, 9H), 1.09 (d, *J* = 6.4 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$) δ =** 178.2, 160.4, 159.3, 108.6, 90.3, 68.3, 55.6, 55.3, 50.5, 38.8, 38.5, 27.1, 16.9. **IR (neat):** ν = 2957, 1729, 1608, 1150 cm^{-1}. **HRMS (ESI):** Calculated for $C_{18}H_{30}NO_5$ ($[M+H]^+$): 340.2118; found: 340.2119

(*S*)-1-phenyl-*N*-(2,4,6-trimethoxybenzyl)ethan-1-amine 4.13i

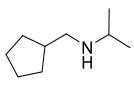


Chemical Formula: $C_{18}H_{23}NO_3$
Exact Mass: 301.1678

Following general procedure **B**, 2,4,6-trimethoxybenzaldehyde (1.38 g, 7.03 mmol, 1 equiv), (*S*)-1-phenylethan-1-amine (900 mg, 7.03 mmol, 1 equiv), AcOH (0.804 mL, 14.06 mmol, 2 equiv) and. $NaBH(OAc)_3$ (2.98 g, 14.06 mmol, 2 equiv) were reacted in DCE (14 mL) overnight. The crude mixture was purified by chromatography on silica gel using DCM/MeOH as eluent, yielding (*S*)-1-phenyl-*N*-(2,4,6-trimethoxybenzyl)ethan-1-amine **4.13i** (1.75 g, 5.8 mmol, 82 %).

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 7.40 – 7.27 (m, 4H), 7.27 – 7.17 (m, 1H), 6.10 (s, 2H), 3.79 (s, 3H), 3.75 (s, 6H), 3.66 (s, 2H), 2.15 (s, 1H), 1.33 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR ($CDCl_3$, 101 MHz) :** δ = 160.4, 159.5, 146.3, 128.2, 127.0, 126.7, 109.3, 90.5, 57.3, 55.6, 55.4, 39.5, 24.5. **IR (neat):** ν = 2923, 2857, 1613 cm^{-1}. **HRMS (ESI):** Calculated for $C_{18}H_{24}NO_3$ ($[M+H]^+$): 302.1756; found: 302.1758

***N*-(cyclopentylmethyl)propan-2-amine 4.13k**



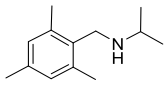
Chemical Formula: $C_9H_{19}N$
Exact Mass: 141.1517

Following general procedure **C**, cyclopentanecarboxaldehyde (1 g, 10.2 mmol, 1 equiv), isopropylamine (0.874 mL, 10.2 mmol, 1 equiv) and Pd/C (1.09 g, 10% w/w, 10 mol%) were reacted in MeOH (25 mL) and stirred overnight under H_2 atmosphere. The crude was then

filtered through celite, and the solvent evaporated to provide *N*-(cyclopentylmethyl)propan-2-amine **4.13k** as a yellowish oil (1.30 g, 9.18 mmol, 90 %).

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 2.78 (hept, *J* = 6.2 Hz, 1H), 2.52 (d, *J* = 7.1 Hz, 2H), 2.08 – 1.89 (m, 1H), 1.85 – 1.68 (m, 3H), 1.65 – 1.48 (m, 4H), 1.22 – 1.09 (m, 2H), 1.06 (d, *J* = 6.2 Hz, 6H). **^{13}C NMR ($CDCl_3$, 101 MHz):** δ = 53.3, 48.9, 40.1, 30.9, 25.2, 22.8. **IR (neat):** ν = 2953, 2867, 1452, 730 cm^{-1}. **HRMS (ESI):** Calculated for $C_9H_{20}N$ ($[M+H]^+$): 142.1590; found: 142.1592

***N*-(2,4,6-trimethylbenzyl)propan-2-amine 4.13l**

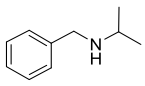


Chemical Formula: $C_{13}H_{21}N$
Exact Mass: 191.1674

Following general procedure **B**, mesitaldehyde (500 mg, 3.37 mmol, 1 equiv), isopropylamine (0.577 mL, 6.74 mmol, 2 equiv), AcOH (0.385 mL, 6.74 mmol, 2 equiv) and. $NaBH(OAc)_3$ (1.58 g, 6.74 mmol, 2 equiv) were reacted in DCE (10 mL) overnight. The crude was purified by chromatography on silica gel using DCM/MeOH as eluent, yielding *N*-(2,4,6-trimethylbenzyl)propan-2-amine **4.13l** (505 mg, 2.64 mmol, 78 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.85 (s, 2H), 4.48 (d, *J* = 14.7 Hz, 1H), 4.34 (d, *J* = 14.7 Hz, 1H), 3.47 – 3.40 (m, 1H), 3.01 (dd, *J* = 14.4, 5.0 Hz, 1H), 2.48 – 2.42 (m, 1H), 2.33 (s, 6H), 2.26 (s, 3H), 1.06 (d, *J* = 6.1 Hz, 3H). **^{13}C NMR ($CDCl_3$, 101 MHz):** δ = 166.8, 137.6, 137.4, 129.4, 128.5, 47.6, 44.1, 38.9, 21.0, 20.1, 19.4. **IR (neat):** ν = 2965, 2361 cm^{-1}. **HRMS (ESI):** Calculated for $C_{13}H_{22}N$ ($[M+H]^+$): 192.1747; found: 192.1749

***N*-benzylpropan-2-amine 4.13n**

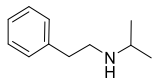


Chemical Formula: $C_{10}H_{15}N$
Exact Mass: 149.1204

Following general procedure **A**, isopropylamine (3.62 mL, 42.3 mmol, 3 equiv), benzaldehyde (1.5 g, 14.1 mmol, 1 equiv), were reacted in THF (10 mL) for 4h with 4Å molecular sieves (5 g, 14 mmol). $NaBH_4$ (1.6 g, 42.3 mmol, 3 equiv) in EtOH (10 mL) was carefully added and the mixture was stirred overnight. The crude was purified by chromatography on silica gel using DCM/MeOH as eluent to provide *N*-benzylpropan-2-amine **4.13n** as a yellowish oil (400 mg, 2.68 mmol, 19 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 – 7.20 (m, 5H), 3.78 (s, 2H), 2.86 (hept, 1H), 1.46 (br. s, 1H), 1.10 (d, *J* = 6.3 Hz, 6H). **^{13}C NMR ($CDCl_3$, 101 MHz):** δ = 140.9, 128.5, 128.2, 127.0, 51.8, 48.2, 23.0 **IR (neat):** ν = 2964, 2362, 1453, 1171 cm^{-1}. **HRMS (ESI):** Calculated for $C_{10}H_{16}N$ ($[M+H]^+$): 150.1283; found: 150.1284

***N*-phenethylpropan-2-amine 4.13o**

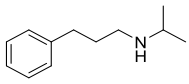


Chemical Formula: $C_{11}H_{17}N$
Exact Mass: 163.1361

Following general procedure **C**, acetone (1.17 mL, 15.9 mmol, 1 equiv), 2-phenylethan-1-amine (2 mL, 15.9 mmol, 1 equiv) and Pd/C (1.69 g, 10% w/w, 10 mol%) were reacted in MeOH (15 mL) and stirred overnight under H_2 atmosphere. The crude was then filtered through celite, and the solvent evaporated to provide *N*-phenethylpropan-2-amine **4.13o** (2.4 g, 14.6 mmol, 92 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 – 7.11 (m, 5H), 2.93 – 2.68 (m, 5H), 1.10 (br. s, 1H), 1.03 (d, *J* = 6.3 Hz, 6H). **^{13}C NMR ($CDCl_3$, 101 MHz):** δ = 140.0, 128.6, 128.4, 126.0, 48.7, 48.5, 36.5, 22.9. **IR (neat):** ν = 2962, 2825, 1473, 1173, 697 cm^{-1}. **HRMS (ESI):** Calculated for $C_{11}H_{18}N$ ($[M+H]^+$): 164.1434; found: 164.1437

***N*-isopropyl-3-phenylpropan-1-amine 4.13p**

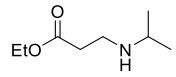


Chemical Formula: $C_{12}H_{19}N$
Exact Mass: 177.1517

Following general procedure **B**, 3-phenylpropionaldehyde (2 g, 14.9 mmol, 1 equiv), isopropylamine (3.83 mL, 44.7 mmol, 3 equiv), AcOH (1.7 mL, 29.8 mmol, 2 equiv) and. $NaBH(OAc)_3$ (6.32 g, 29.8 mmol, 2 equiv) were reacted in DCE (75 mL) overnight. The crude mixture was purified by chromatography on silica gel using DCM/MeOH as eluent, yielding *N*-isopropyl-3-phenylpropan-1-amine **4.13p** (2 g, 11.3 mmol, 76 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 – 7.26 (m, 2H), 7.21 (d, *J* = 7.3 Hz, 3H), 2.80 (hept, *J* = 6.3 Hz, 1H), 2.72 – 2.62 (m, 4H), 1.90 – 1.79 (m, 2H), 1.20 (br. s, 1H), 1.07 (d, *J* = 6.3 Hz, 6H). **^{13}C NMR ($CDCl_3$, 101 MHz):** δ = 142.3, 128.5, 128.4, 125.9, 48.8, 47.3, 34.0, 32.2, 23.1. **IR (neat):** ν = 2964, 2861, 1473, 699 cm^{-1}. **HRMS (ESI):** Calculated for $C_{12}H_{20}N$ ($[M+H]^+$): 178.1590; found: 178.1592

Ethyl 3-(isopropylamino)propanoate 4.13q

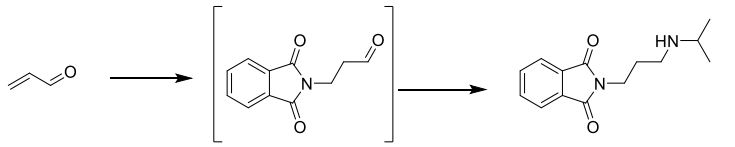


Chemical Formula: $C_8H_{17}NO_2$
Exact Mass: 159.1259

To a solution of isopropylamine (20 mmol, 1.18 g, 2.0 equiv) in ethanol (13 mL) at 0°C was added, via addition funnel, a solution of ethyl acrylate (10 mmol, 1 g, 1.0 equiv) in ethanol (7 mL). The reaction mixture was allowed to warm to ambient temperature then stirred at ambient temperature for 24 h, concentrated under vacuum. The excess of amine was removed under high vacuum to provide Ethyl 3-(isopropylamino)propanoate **4.13q** (1.59 g, 10 mmol, 100 %).

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 4.14 (q, *J* = 7.1 Hz, 2H), 2.92 – 2.72 (m, 3H), 2.49 (t, *J* = 6.6 Hz, 2H), 1.33 – 1.21 (m, 4H), 1.05 (d, *J* = 6.2 Hz, 6H). **^{13}C NMR ($CDCl_3$, 101 MHz):** δ = 172.8, 60.3, 48.4, 42.5, 35.0, 22.9, 14.2. **IR (neat):** ν = 1732 1191 cm^{-1}. **HRMS (ESI):** Calculated for $C_8H_{18}NO_2$ ($[M+H]^+$): 160.1332; found: 160.1331

2-(3-(isopropylamino)propyl)isoindoline-1,3-*di*one 4.13r



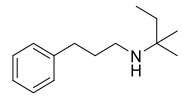
Chemical Formula: $C_{14}H_{18}N_2O_2$
Exact Mass: 246.1368

75 %

3-Phthalimidopropionaldehyde was prepared following an analogous procedure described by T. Livinghouse. Acroleine (561 mg, 10 mmol, 1 equiv) and phtalimid (1.47 g, 10 mmol, 1 equiv) were suspended in AcOEt (6.5 mL) and stirred at 65 °C for 10 minutes. Then, Triton B (40 % solution of benzyltrimethylammonium hydroxide in MeOH, 90 µL, 0.2 mmol, 2 mol%) was added to the solution, which was further stirred for 20 minutes. The mixture was then cooled to room temperature, the solvent removed under vacuum and the resulting yellowish solid triturated with Et_2O. The resulting solid was then filtered to provide 3-Phthalimidopropionaldehyde (2.02 g, 10 mmol, 100 %). Then, following general procedure C, 3-Phthalimidopropionaldehyde (2.02 g, 10 mmol, 1 equiv), isopropylamine (0.852 mL, 10 mmol, 1 equiv) and Pd/C (1.06 g, 10% w/w, 10 mol%) were reacted in MeOH (25 mL) and stirred overnight under H_2 atmosphere. The crude was then filtered through celite, and the solvent evaporated to provide 2-(3-(isopropylamino)propyl)isoindoline-1,3-dione **4.13r** as a yellowish oil (1.84 g, 7.5 mmol, 75 %). Prepared according to the described literature [188].

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 7.88 – 7.81 (m, 2H), 7.76 – 7.66 (m, 2H), 3.76 (t, *J* = 6.8 Hz, 2H), 2.75 (hept, *J* = 6.2 Hz, 1H), 2.62 (t, *J* = 7.0 Hz, 2H), 1.94 – 1.79 (m, 3H), 1.03 (d, *J* = 6.2 Hz, 6H). **^{13}C NMR ($CDCl_3$, 101 MHz) :** δ = 168.5, 133.9, 132.2, 123.2, 48.7, 44.3, 36.0, 29.2, 22.9. **IR (neat):** ν = 1773, 1705, 1468, 1442 cm^{-1}. **HRMS (ESI):** Calculated for $C_{14}H_{19}N_2O_2$ ($[M+H]^+$): 247.1441; found: 247.1442

2-methyl-*N*-(3-phenylpropyl)butan-2-amine 4.13s

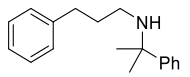


Chemical Formula: $C_{14}H_{23}N$
Exact Mass: 205.1830

Following general procedure **B**, 3-phenylpropionaldehyde (1 g, 7.45 mmol, 1 equiv), tert-amylamine (2.61 mL, 22.4 mmol, 3 equiv), AcOH (0.852 mL, 14.9 mmol, 2 equiv) and. $NaBH(OAc)_3$ (3.16 g, 14.9 mmol, 2 equiv) were reacted in DCE (37 mL) overnight. The crude mixture was purified by chromatography on silica gel using DCM/MeOH as eluent, yielding 2-methyl-*N*-(3-phenylpropyl)butan-2-amine **4.13s** (1.35 g, 6.57 mmol, 88 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 – 7.13 (m, 5H), 3.73 (s, 1H), 2.72 – 2.62 (m, 2H), 2.60 – 2.47 (m, 2H), 1.86 – 1.69 (m, 2H), 1.47 – 1.32 (m, 2H), 1.01 (s, 6H), 0.82 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR ($CDCl_3$, 101 MHz) :** δ = 142.2, 128.3, 128.2, 125.6, 52.3, 41.5, 33.8, 33.0, 32.6, 26.5, 8.2. **IR (neat):** ν = 3028, 2935, 1475, 1442 cm^{-1}. **HRMS (ESI):** Calculated for $C_{14}H_{24}N$ ($[M+H]^+$): 206.1903; found: 206.1902

3-phenyl-*N*-(2-phenylpropan-2-yl)propan-1-amine 4.13t



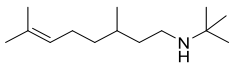
Chemical Formula: $C_{18}H_{23}N$
Exact Mass: 253.1830

Following general procedure **B**, phenylpropionaldehyde (500 mg, 3.73 mmol, 1 equiv), cumylamine (504 mg, 3.73 mmol, 1 equiv), AcOH (0.427 mL, 7.46 mmol, 2 equiv) and. $NaBH(OAc)_3$ (1.58 g, 7.1 mmol, 2 equiv) were reacted in DCE (19 mL) overnight. The crude mixture was purified by chromatography on silica gel using DCM/MeOH as eluent, yielding 3-phenyl-*N*-(2-phenylpropan-2-yl)propan-1-amine **4.13t** (832 mg, 3.28 mmol, 88 %).

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 7.46 – 7.41 (m, 2H), 7.36 – 7.30 (m, 2H), 7.27 – 7.19 (m, 3H), 7.18 – 7.10 (m, 3H), 2.62 – 2.55 (m, 2H), 2.38 (t, *J* = 7.1 Hz, 2H), 1.82 – 1.70 (m, 2H), 1.47 (s, 6H).

^{13}C NMR ($CDCl_3$, 101 MHz) : δ = 142.3, 128.5, 128.4, 128.3, 126.4, 125.9, 125.8, 56.2, 42.8, 33.8, 32.5, 29.6. **IR (neat):** ν = 3026, 2928, 1495, 1452, 699 cm^{-1}. **HRMS (ESI)** : Calculated for $C_{18}H_{24}N$ ($[M+H]^+$): 254.1903; found: 254.1908

<u>*N*-(tert-butyl)-3,7-*di*methyloct-6-en-1-amine 4.13u</u>

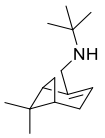


Chemical Formula: $C_{14}H_{29}N$
Exact Mass: 211.2300

Following general procedure **B**, (±)-citronellal (1.66 g, 10 mmol, 1 equiv), *tert*-butylamine (1.06 mL, 10 mmol, 1 equiv), AcOH (1.14 mL, 20 mmol, 2 equiv) and. $NaBH(OAc)_3$ (4.23 g, 20 mmol, 2 equiv) were reacted in DCE (25 mL) overnight. The crude was purified by chromatography on silica gel using DCM/MeOH as eluent, yielding *N*-(tert-butyl)-3,7-dimethyloct-6-en-1-amine **4.13u** (1.77 g, 8.4 mmol, 84 %).

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 5.08 – 4.99 (m, 1H), 2.59 – 2.38 (m, 2H), 1.99 – 1.85 (m, 2H), 1.62 (d, *J* = 1.3 Hz, 3H), 1.53 (s, 3H), 1.48 – 1.07 (m, 6H), 1.04 (s, 9H), 0.83 (d, *J* = 6.3 Hz, 3H). **^{13}C NMR ($CDCl_3$, 101 MHz) :** δ = 131.1, 124.9, 50.3, 40.4, 38.3, 37.3, 30.8, 29.1, 25.8, 25.5, 19.7, 17.7. **IR (neat):** ν = 2964, 2917, 2362, 1449, 731 cm^{-1}. **HRMS (ESI):** Calculated for $C_{14}H_{30}N$ ($[M+H]^+$): 212.2378; found: 212.2379

<u>*N*-(((1*S*,5*R*)-6,6-*di*methylbicyclo[3.1.1]hept-2-en-3-yl)methyl)-2-methylpropan-2-amine 4.13v</u>



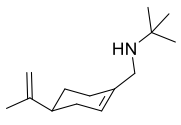
Chemical Formula: $C_{14}H_{25}N$
Exact Mass: 207.1987

Following general procedure **B**, (-)-Myrtenal (800 mg, 5.33 mmol, 1 equiv), *tert*-butylamine (0.565 mL, 5.33 mmol, 1 equiv), AcOH (0.610 mL, 10.7 mmol, 2 equiv) and. $NaBH(OAc)_3$ (2.26 g, 10.7 mmol, 2 equiv) were reacted in DCE (25 mL) overnight. The crude was purified by chromatography on silica gel using DCM/MeOH as eluent, yielding *N*-(((1*S*,5*R*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-3-yl)methyl)-2-methylpropan-2-amine **4.13v** (970 mg, 4.69 mmol, 88 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.41 – 5.35 (m, 1H), 3.12 – 3.02 (m, 2H), 2.36 (dt, *J* = 8.5, 5.6 Hz, 1H), 2.30 – 2.15 (m, 2H), 2.06 (dd, *J* = 5.7, 1.6 Hz, 2H), 1.26 (s, 3H), 1.18 (d, *J* = 8.6 Hz, 1H), 1.12 (s, 9H), 0.81 (s, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 146.6, 117.1, 50.9, 47.9, 45.1, 41.0, 38.2, 31.7, 31.3, 28.9, 26.4, 21.2. **IR (neat):** ν = 2960, 2913, 1483, 733 cm^{-1}. **HRMS (ESI):** Calculated for $C_{14}H_{26}N$ ($[M+H]^+$): 208.2060; found: 208.2061

(*S*)-2-methyl-*N*-((4-(prop-1-en-2-yl)cyclohex-1-en-1-yl)methyl)propan-2-amine 4.13w

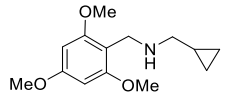


Chemical Formula: $C_{14}H_{25}N$
Exact Mass: 207.1987

Following general procedure **B**, (-)-perillaldehyde (1.5 g, 10 mmol, 1 equiv), *tert*-butylamine (1.06 mL, 10 mmol, 1 equiv), AcOH (1.15 mL, 20 mmol, 2 equiv) and. $NaBH(OAc)_3$ (4.23 g, 20 mmol, 2 equiv) were reacted in DCE (25 mL) overnight. The crude was purified by chromatography on silica gel using DCM/MeOH as eluent, yielding (*S*)-2-methyl-*N*-((4-(prop-1-en-2-yl)cyclohex-1-en-1-yl)methyl)propan-2-amine **4.13w** (1.84 g, 8.9 mmol, 89 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.64 – 5.57 (m, 1H), 4.73 – 4.64 (m, 2H), 3.13 – 3.00 (m, 2H), 2.19 – 2.04 (m, 4H), 2.00 – 1.89 (m, 1H), 1.87 – 1.76 (m, 1H), 1.75 – 1.70 (m, 3H), 1.59 – 1.35 (m, 2H), 1.11 (s, 9H). **^{13}C NMR ($CDCl_3$, 101 MHz) :** δ = 150.2, 136.7, 121.5, 108.6, 50.6, 48.8, 41.4, 30.8, 29.1, 28.1, 20.9. **IR (neat):** ν = 2960, 2922, 1463, 790 cm^{-1}. **HRMS (ESI):** Calculated for $C_{14}H_{26}NO$ ($[M+H]^+$): 208.2060; found: 208.2062

1-cyclopropyl-*N*-(2,4,6-trimethoxybenzyl)methanamine 4.13y



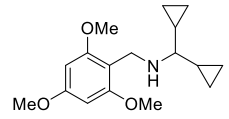
Chemical Formula: $C_{14}H_{21}NO_3$
Exact Mass: 251.1521

Following general procedure **B**, 2,4,6-trimethoxybenzaldehyde (1 g, 5.1 mmol, 1 equiv), cyclopropylmethanamine (0.445 mL, 5.1 mmol, 1 equiv), AcOH (0.583 mL, 10.2 mmol, 2 equiv) and. $NaBH(OAc)_3$ (2.16 g, 10.2 mmol, 2 equiv) were reacted in DCE (25 mL) overnight. The crude was purified by chromatography on silica gel using DCM/MeOH as eluent, yielding 1-cyclopropyl-*N*-(2,4,6-trimethoxybenzyl)methanamine **4.13y** (1.25 g, 5.0 mmol, 98 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.10 (s, 2H), 3.81 – 3.75 (m, 11H), 2.44 (br. s, 1H), 2.41 (d, *J* = 7.0 Hz, 2H), 1.03 – 0.92 (m, 1H), 0.47 – 0.39 (m, 2H), 0.10 – 0.02 (m, 2H). **^{13}C NMR ($CDCl_3$, 101 MHz) :** δ = 160.4, 159.4, 109.0, 90.5, 55.7, 55.4, 54.1, 41.3, 11.4, 3.5.

IR (neat): ν = 3000, 2362, 1604, 1459, 1130 cm^{-1}. **HRMS (ESI):** Calculated for $C_{14}H_{22}NO_3$ ($[M+H]^+$): 252.1594; found: 252.1597

1,1-dicyclopropyl-*N*-(2,4,6-trimethoxybenzyl)methanamine 4.13z

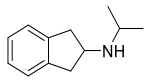


Chemical Formula: $C_{17}H_{25}NO_3$
Exact Mass: 291.1834

Following general procedure **B**, 2,4,6-trimethoxybenzaldehyde (697 mg, 3.55 mmol, 1 equiv), dicyclopropylmethanamine (395 mg, 3.55 mmol, 1 equiv), AcOH (0.406 mL, 7.1 mmol, 2 equiv) and $NaBH(OAc)_3$ (1.5 g, 7.1 mmol, 2 equiv) were reacted in DCE (18 mL) overnight. The crude was purified by chromatography on silica gel using DCM/MeOH as eluent, yielding 1,1-dicyclopropyl-*N*-(2,4,6-trimethoxybenzyl)methanamine **4.13z** (847 mg, 2.91 mmol, 82 %).

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 6.08 (s, 2H), 3.86 (s, 2H), 3.81 – 3.75 (m, 9H), 1.04 (t, *J* = 8.6 Hz, 1H), 0.96 – 0.85 (m, 2H), 0.48 – 0.37 (m, 4H), 0.20 – 0.07 (m, 4H). **^{13}C NMR ($CDCl_3$, 101 MHz) :** δ = 160.3, 159.3, 109.0, 90.4, 67.0, 55.6, 55.4, 40.2, 16.2, 2.8, 2.2 . **IR (neat):** ν = 3001, 2939, 1604, 1459, 1149 cm^{-1}. **HRMS (ESI):** Calculated for $C_{17}H_{26}NO_3$ ($[M+H]^+$): 292.1907; found: 292.1911

***N*-isopropyl-2,3-*d*ihydro-1H-inden-2-amine 4.13aa**

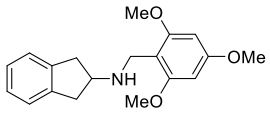


Chemical Formula: $C_{12}H_{17}N$
Exact Mass: 175.1361

Following general procedure **C**, acetone (0.276 mL, 3.75 mmol, 1 equiv), 2,3-dihydro-1H-inden-2-amine (500 mg, 3.75 mmol, 1 equiv) and Pd/C (400 mg, 10% w/w, 10 mol%) were reacted in MeOH (7 mL) and stirred overnight under H_2 atmosphere. The crude was then filtered through celite, and the solvent evaporated to provide *N*-isopropyl-2,3-dihydro-1H-inden-2-amine **4.13aa** (526 mg, 3 mmol, 80 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 – 7.17 (m, 2H), 7.17 – 7.11 (m, 3H), 3.74 (p, *J* = 7.1 Hz, 1H), 3.18 (dd, *J* = 15.4, 7.1 Hz, 2H), 2.98 (hept, *J* = 6.2 Hz, 1H), 2.72 (dd, *J* = 15.4, 7.1 Hz, 2H), 1.27 (br. s, 1H), 1.10 (d, *J* = 6.3 Hz, 6H). **^{13}C NMR ($CDCl_3$, 101 MHz) :** δ = 141.9, 126.5, 124.8, 57.1, 46.6, 40.5, 23.3. **IR (neat):** ν = 2962, 1475, 1175, 741cm^{-1}. **HRMS (ESI):** Calculated for $C_{12}H_{18}N$ ($[M+H]^+$): 176.1434; found: 176.1437

***N*-(2,4,6-trimethoxybenzyl)-2,3-*d*ihydro-1H-inden-2-amine 4.13ab**

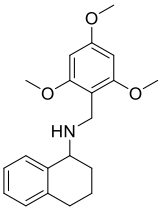


Chemical Formula: $C_{19}H_{23}NO_3$
Exact Mass: 313.1678

Following general procedure **C**, 2,4,6-trimethoxybenzaldehyde (447 mg, 2.28 mmol, 1 equiv), 2,3-dihydro-1H-inden-2-amine (304 mg, 2.28 mmol, 1 equiv) and Pd/C (243 mg, 10% w/w, 10 mol%) were reacted in MeOH (10 mL) and stirred overnight under H_2 atmosphere. The crude was purified by chromatography on silica gel to provide *N*-(2,4,6-trimethoxybenzyl)-2,3-dihydro-1H-inden-2-amine **4.13ab** (215 mg, 0.684 mmol, 30 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 – 7.07 (m, 4H), 6.12 (s, 2H), 3.84 (s, 2H), 3.81 (s, 9H), 3.60 (p, *J* = 6.9 Hz, 1H), 3.15 (dd, *J* = 15.6, 7.1 Hz, 2H), 2.79 (dd, *J* = 15.6, 6.8 Hz, 2H), 1.73 (br. s, 1H). **^{13}C NMR ($CDCl_3$, 101 MHz) :** δ = 160.4, 159.4, 142.4, 126.3, 124.7, 109.4, 90.5, 58.8, 55.8, 55.5, 40.4, 39.9. **IR (neat):** ν = 2937, 2361, 1597, 1131cm^{-1}. **HRMS (ESI):** Calculated for $C_{19}H_{24}NO_3$ ($[M+H]^+$): 314.1751; found: 314.1754

***N*-(2,4,6-trimethoxybenzyl)-1,2,3,4-tetrahydronaphthalen-1-amine 4.13ac**

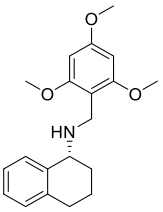


Chemical Formula: $C_{20}H_{25}NO_3$
Exact Mass: 327.1834

Following general procedure **B**, 2,4,6-trimethoxybenzaldehyde (691 mg, 3.52 mmol, 1 equiv), 1,2,3,4-tetrahydronaphthalen-1-amine (518 mg, 3.52 mmol, 1 equiv), AcOH (0.403 mL, 7.04 mmol, 2 equiv) and. $NaBH(OAc)_3$ (1.49 g, 7.04 mmol, 2 equiv) were reacted in DCE (10 mL) overnight. The crude was extracted twice with DCM, dried over sodium sulfate, filtered, evaporated under vacuum, yielding *N*-(2,4,6-trimethoxybenzyl)-1,2,3,4-tetrahydronaphthalen-1-amine **4.13ac** (950 mg, 2.9 mmol, 83 %).

^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.11 – 7.02 (m, 4H), 6.15 (s, 2H), 3.88 (d, *J* = 1.8 Hz, 2H), 3.82 (s, 9H), 3.72 – 3.66 (m, 1H), 2.90 – 2.61 (m, 2H), 2.12 – 1.95 (m, 3H), 1.87 – 1.61 (m, 2H). **^{13}C NMR (63 MHz, $CDCl_3$) δ =** 160.4, 159.6, 140.0, 137.8, 129.0, 128.8, 126.4, 125.7, 109.7, 90.7, 55.8, 55.5, 54.2, 39.4, 29.7, 28.0, 19.0. **IR (neat):** ν = 2936, 2361, 1607, 1131 cm^{-1}. **HRMS (ESI):** Calculated for $C_{20}H_{26}NO_3$ ($[M+H]^+$): 328.1907; found: 328.1912

(*R*)-*N*-(2,4,6-trimethoxybenzyl)-1,2,3,4-tetrahydronaphthalen-1-amine (-)-4.13ac

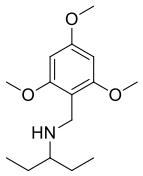


Chemical Formula: $C_{20}H_{25}NO_3$
Exact Mass: 327.1834

Following general procedure **B**, 2,4,6-trimethoxybenzaldehyde (2.67 g, 13.6 mmol, 1 equiv), (*R*)-1,2,3,4-tetrahydronaphthalen-1-amine (2 g, 13.6 mmol, 1 equiv), AcOH (1.56 mL, 27.2 mmol, 2 equiv) and. $NaBH(OAc)_3$ (5.76 g, 27.2 mmol, 2 equiv) were reacted in DCE (30 mL) overnight. Then, the mixture was quenched using a solution of NaOH (1M) and the crude was stirred for further 30 minutes. The crude was extracted twice with DCM, dried over sodium sulfate, filtered, evaporated under vacuum, yielding -(*R*)-*N*-(2,4,6-trimethoxybenzyl)-1,2,3,4-tetrahydronaphthalen-1-amine (-)-**4.13ac** (4.45 g, 13.6 mmol, 100 %).

^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.13 – 7.00 (m, 4H), 6.15 (s, 2H), 3.88 (d, *J* = 1.8 Hz, 2H), 3.82 (s, 9H), 3.72 – 3.65 (m, 1H), 2.94 – 2.59 (m, 2H), 2.22 – 1.93 (m, 3H), 1.88 – 1.51 (m, 2H). **^{13}C NMR (63 MHz, $CDCl_3$) δ =** 160.4, 159.6, 140.0, 137.8, 129.0, 128.8, 126.4, 125.7, 109.7, 90.7, 55.8, 55.5, 54.2, 39.4, 29.7, 28.0, 19.0. **IR (neat):** ν = 2938, 2355, 1635, 1115 cm^{-1}. **HRMS (ESI):** Calculated for $C_{20}H_{26}NO_3$ ($[M+H]^+$): 328.1907; found: 328.1912.

N-(2,4,6-trimethoxybenzyl)pentan-3-amine 4.11af



Chemical Formula: $C_{15}H_{25}NO_3$
Exact Mass: 267,1834

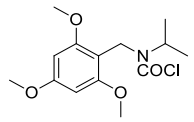
Following general procedure B, 2,4,6-trimethoxybenzaldehyde (1 g, 5.1 mmol, 1 equiv), Pentan-3-amine(0.88 g, 10.2 mmol, 2 equiv), AcOH (0.58 mL, 10.2 mmol, 2 equiv) and $NaBH(OAc)_3$ (2.16 g, 10.2 mmol, 2 equiv) were reacted in DCE (25mL) overnight. The crude mixture was extracted twice with DCM, dried over sodium sulfate, filtered, evaporated under vacuum, yielding N-(2,4,6-trimethoxybenzyl)pentan-3-amine **4.11af** as a slighly yellow oil (1.02 g, 3.8 mmol, 75%).

^{1}H NMR (250 MHz, $CDCl_3$) δ = 6.07 (s, 2H), 3.76 (s, 3H), 3.76 (s, 6H), 3.71 (s, 2H), 2.20 (p, *J* = 6.0 Hz, 1H), 1.91 (s, 1H), 1.46 –1.26 (m, 4H), 0.81 (t, J = 7.5 Hz, 6H).

^{13}C NMR (63 MHz, $CDCl_3$) δ = 160.2, 159.4, 109.7, 90.5, 59.3, 55.7, 55.4, 38.8, 26.1, 10.2. **IR (neat):** ν = 2928, 2840, 1623, 1139 **HRMS (ESI):** Calculated for $C_{20}H_{26}NO_3$([M+H]+): 269.1913; found: 269.1917

3.8. Carbamoyl's synthesis

Isopropyl(2,4,6-trimethoxybenzyl)carbamoyl chloride 4.11a

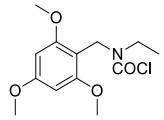


Chemical Formula: $C_{14}H_{20}ClNO_4$

Following general procedure **carbamoyl chloride**, *N*-(2,4,6-trimethoxybenzyl)propan-2-amine **4.13a** (800 mg, 3.34 mmol 1 equiv), Et_3N (0.560 mL, 4.01 mmol, 1.2 equiv) and triphosgene (337 mg, 1.14 mmol, 0.34 equiv) were reacted in in dry benzene (16 mL) at 0 °C . The desired Isopropyl(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11a** was obtained as a grey solid (792 mg, 2.74 mmol, 82 %) and used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.11 (s, 2H), 4.72 (s, 2H), 3.83 – 3.82 (m, 9H), 3.57 (sep, *J* = 6.8 Hz, 1H), 1.11 (d, *J* = 6.8 Hz, 6H).

Ethyl(2,4,6-trimethoxybenzyl)carbamoyl chloride 4.11b

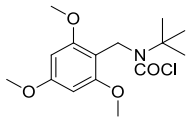


Chemical Formula: $C_{13}H_{18}ClNO_4$

Following general procedure **carbamoyl chloride**, *N*-(2,4,6-trimethoxybenzyl)ethanamine **4.11b** (401 mg, 1.78 mmol, 1 equiv), Et_3N (0.301 mL, 2.14 mmol, 1.2 equiv) and triphosgene (180 mg, 0.60 mmol, 0.34 equiv) were reacted in dry benzene (9 mL) at 0 °C . The desired Ethyl(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11b** was obtained as a white solid (472 mg, 1.64 mmol, 92 %) and used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.11 (s, 2H), 4.69 – 4.66 (m, 2H), 3.82 (s, 3H), 3.81 (s, 6H), 3.31 – 3.17 (m, 2H), 1.06 – 1.01 (m, 3H).

***Tert*-butyl(2,4,6-trimethoxybenzyl)carbamoyl chloride 4.11c**

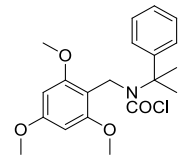


Chemical Formula: $C_{15}H_{22}ClNO_4$

Following general procedure **carbamoyl chloride**, 2-methyl-*N*-(2,4,6-trimethoxybenzyl)propan-2-amine **4.13 c**(400 mg, 1.58 mmol, 1 equiv), Et_3N (0.267 mL, 1.90 mmol, 1.2 equiv) and triphosgene (159 mg, 0.537 mmol, 0.34 equiv) were reacted in dry benzene (8 mL) at 0 °C . The desired Tert-butyl(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11c** was obtained as a yellowish oil (229 mg, 0.73 mmol, 46 %) and used without further purification.

^{1}H NMR (250 MHz, $CDCl_3$) δ = 6.07 (s, 2H), 4.12 – 4.04 (m, 2H), 3.87 (s, 6H), 3.78 (s, 3H), 1.33 (s, 9H).

(2-phenylpropan-2-yl)(2,4,6-trimethoxybenzyl)carbamoyl chloride 4.11d

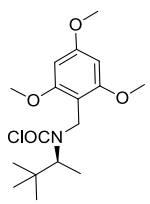


Chemical Formula: $C_{20}H_{24}ClNO_4$

Following general procedure **carbamoyl chloride**, 2-phenyl-*N*-(2,4,6-trimethoxybenzyl)propan-2-amine **4.13d** (400 mg, 1.27 mmol, 1 equiv), Et_3N (0.214 mL, 1.52 mmol, 1.2 equiv) and triphosgene (128 mg, 0.432 mmol, 0.34 equiv) were reacted in dry benzene (7.6mL) at 0 °C . The desired (2-phenylpropan-2-yl)(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11d** was obtained as an orange oil (341 mg, 0.9 mmol, 71 %) and used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.70 – 7.61 (m, 2H), 7.41 – 7.36 (m, 3H), 5.93 (s, 2H), 3.81 (s, 6H), 3.70 (s, 3H), 1.83 (s, 6H).

(*S*)-(3,3-*d*imethylbutan-2-yl)(2,4,6-trimethoxybenzyl)carbamoyl chloride 4.11e



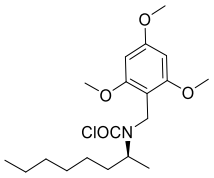
Chemical Formula: $C_{17}H_{26}ClNO_4$

Following general procedure **carbamoyl chloride**, (*S*)-3,3-dimethyl-N-(2,4,6-trimethoxybenzyl)butan-2-amine **4.13e** (300 mg, 1.07 mmol, 1 equiv), Et_3N (0.180 mL, 1.28

mmol, 1.2 equiv) and triphosgene (108 mg, 0.367 mmol, 0.34 equiv) were reacted in dry benzene (5.4 mL) at 0 °C. The desired (S)-(3,3-dimethylbutan-2-yl)(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11e** was obtained as a greenish solid (304 mg, 0.89 mmol, 84 %) and used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.16 – 6.10 (m, 2H), 5.04 – 4.45 (m, 2H), 3.87 – 3.78 (m, 9H), 3.16 – 2.35 (m, 1H), 1.42 – 1.02 (m, 3H), 0.99 – 0.90 (m, 9H).

(*S*)-octan-2-yl(2,4,6-trimethoxybenzyl)carbamoyl chloride 4.11f

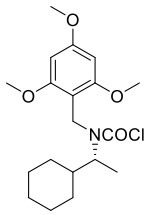


Chemical Formula: $C_{19}H_{30}ClNO_4$

Following general procedure for the synthesis of carbamoyl chloride, (*S*)-N-(2,4,6-trimethoxybenzyl)octan-2-amine **4.13f** (400 mg, 2.45 mmol, 1 equiv), Et_3N (0.413 mL, 2.94 mmol, 1.2 equiv) and triphosgene (247 mg, 0.833 mmol, 0.34 equiv) were reacted in dry benzene (15 mL) at 0 °C . The desired (*S*)-octan-2-yl(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11f** was obtained as a yellowish solid (515 mg, 2.28 mmol, 93 %) and used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.12 – 6.10 (m, 2H), 4.78 – 4.64 (m, 2H), 3.82 (s, 3H), 3.82 (s, 6H), 3.32 (dt, *J* = 8.1, 6.4 Hz, 1H), 1.84 – 1.72 (m, 1H), 1.46 – 1.33 (m, 1H), 1.30 – 1.10 (m, 8H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.86 (t, *J* = 7.0 Hz, 3H).

(*R*)-(1-cyclohexylethyl)(2,4,6-trimethoxybenzyl)carbamoyl chloride 4.11g



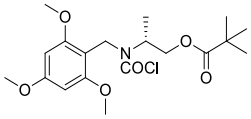
Chemical Formula: $C_{19}H_{28}ClNO_4$

Following general procedure **carbamoyl chloride**, (*R*)-1-cyclohexyl-N-(2,4,6-trimethoxybenzyl)ethan-1-amine **4.13g** (600 mg, 1.95 mmol, 1 equiv), Et_3N (0.329 mL, 2.34 mmol, 1.2 equiv) and triphosgene (197 mg, 0.663 mmol, 0.34 equiv) were reacted in dry benzene (10 mL) at 0 °C .

The desired (*R*)-(1-cyclohexylethyl)(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11g** was obtained as a red oil (528 mg, 1.42 mmol, 73 %) and used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.11 (s, 2H), 4.82 (d, *J* = 14.2 Hz, 1H), 4.57 (d, *J* = 14.1 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 6H), 2.89 (dq, *J* = 10.2, 6.7 Hz, 1H), 1.96 – 1.85 (m, 1H), 1.78 – 1.60 (m, 4H), 1.26 – 1.04 (m, 4H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.75 – 0.52 (m, 2H).

(*R*)-2-((chlorocarbonyl)(2,4,6-trimethoxybenzyl)amino)propyl pivalate 4.11h

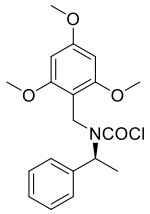


Chemical Formula: $C_{19}H_{28}ClNO_6$

Following general procedure **carbamoyl chloride**, (*R*)-2-((2,4,6-trimethoxybenzyl)amino)propyl pivalate **4.13h** (188 mg, 0.553 mmol, 1 equiv), Et_3N (0.093 mL, 0.66 mmol, 1.2 equiv) and triphosgene (56 mg, 0.188 mmol, 0.34 equiv) were reacted in dry benzene (2.8 mL) at 0 °C . The desired (*R*)-2-((chlorocarbonyl)(2,4,6-trimethoxybenzyl)amino)propyl pivalate **4.11h** was obtained as a brownish solid (190 mg, 0.47 mmol, 85 %) and used without further purification.

^{1}H NMR (250 MHz, $CDCl_3$) δ = 6.11 (s, 2H), 4.90 (d, *J* = 14.3 Hz, 1H), 4.62 (d, *J* = 14.3 Hz, 1H), 4.33 (dd, *J* = 11.2, 9.1 Hz, 1H), 4.07 (dd, *J* = 11.2, 5.3 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 6H), 3.73 – 3.59 (m, 1H), 1.21 (s, 9H), 0.99 (d, *J* = 6.9 Hz, 3H).

(*S*)-(1-phenylethyl)(2,4,6-trimethoxybenzyl)carbamoyl chloride 4.11i

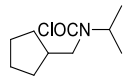


Chemical Formula: $C_{19}H_{22}ClNO_4$

Following general procedure **carbamoyl chloride**, (*S*)-1-phenyl-*N*-(2,4,6-trimethoxybenzyl)ethan-1-amine **4.13i** (300 mg, 0.995 mmol, 1 equiv), Et_3N (0.167 mL, 1.19 mmol, 1.2 equiv) and triphosgene (100 mg, 0.338 mmol, 0.34 equiv) were reacted in dry benzene (7.8 mL) at 0 °C . The desired (S)-(1-phenylethyl)(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11i** was obtained as a brownish solid (325 mg, 0.9 mmol, 90 %) and used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.24 – 7.16 (m, 5H), 6.09 – 5.98 (m, 2H), 4.89 – 4.80 (m, 2H), 4.74 – 4.64 (m, 1H), 3.81 (s, 3H), 3.78 (s, 6H), 1.50 (d, *J* = 7.1 Hz, 3H).

(cyclopentylmethyl)(isopropyl)carbamoyl chloride 4.11k

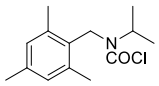


Chemical Formula: $C_{10}H_{18}ClNO$

Following general procedure **carbamoyl chloride**, *N*-(cyclopentylmethyl)propan-2-amine **4.13k** (400 mg, 2.83 mmol, 1 equiv), Et_3N (0.477 mL, 3.40 mmol, 1.2 equiv) and triphosgene (286 mg, 0.962 mmol, 0.34 equiv) were reacted in dry benzene (17 mL) at 0 °C . The desired (cyclopentylmethyl)(isopropyl)carbamoyl chloride **4.11k** was obtained as a yellowish oil (507 mg, 2.49 mmol, 88 %) and used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.55 – 3.77 (m, 1H), 3.40 – 3.20 (m, 2H), 2.28 – 2.15 (m, 1H), 1.82 – 1.50 (m, 8H), 1.37 – 1.19 (m, 6H).

Isopropyl(2,4, 6-trimethylbenzyl)carbamoyl chloride 4.11l

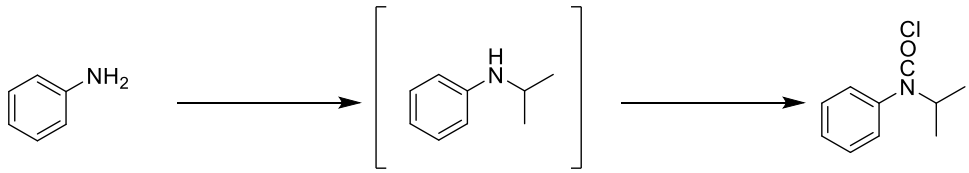


Chemical Formula: $C_{14}H_{20}ClNO$

Following general procedure **carbamoyl chloride**, *N*-isopropyl-3-phenylpropan-1-amine **4.13l** (400 mg, 2.09 mmol, 1 equiv), Et_3N (0.352 mL, 2.51 mmol, 1.2 equiv) and triphosgene (211 mg, 0.711 mmol, 0.34 equiv) were reacted in dry benzene (10.4 mL) at 0 °C The desired Isopropyl(2,4, 6-trimethylbenzyl)carbamoyl chloride **4.11l** was obtained as a brownish solid (418 mg, 1.65 mmol, 79 %) and used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.87 (s, 2H), 4.76 (s, 2H), 3.23 – 3.10 (m, 1H), 2.33 (s, 6H), 2.28 (s, 3H), 1.20 (d, *J* = 6.8 Hz, 6H).

Isopropyl(phenyl)carbamoyl chloride 4.11m



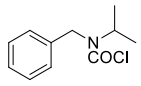
Chemical Formula: $C_{10}H_{12}ClNO$

Following general procedure **A**, aniline (130 mg, 1.4 mmol, 1 equiv), acetone (0.103 mL, 1.4 mmol, 1 equiv) and 4Å molecular sieves (200 mg) were stirred for 4h in THF (14 mL). Then, a solution of $NaBH_4$ (106 mg, 2.8 mmol, 2 equiv) in EtOH (5 mL) was carefully added to the mixture. The reaction was stirred at room temperature overnight, and was then filtered through

celite. The crude was then acidified using a solution of HCl (0.1M) and stirred for 30 minutes. The mixture was then basified using NaOH solution (0.1M) and extracted three times using AcOEt. The combined organic layers were dried over sodium sulfate, filtered and evaporated under vacuum. Following general procedure **carbamoyl chloride**, *N*-isopropylaniline (189 mg, 1.4 mmol, 1 equiv), Et_3N (0.236 mL, 1.36 mmol, 1.2 equiv) and triphosgene (141 mg, 2.01 mmol, 0.34 equiv) were reacted in dry benzene (7 mL) at 0 °C. The desired Isopropyl(phenyl)carbamoyl chloride **4.11m** was obtained as a yellowish solid (218 mg, 1.1 mmol, 79 %) and used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45 – 7.39 (m, 2H), 7.18 – 7.14 (m, 2H), 4.68 (sep, *J* = 6.8 Hz, 1H), 1.17 (d, *J* = 6.8 Hz, 6H).

Benzyl(isopropyl)carbamoyl chloride 4.11n

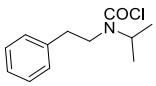


Chemical Formula: $C_{11}H_{14}ClNO$

Following general procedure **carbamoyl chloride**, *N*-benzylpropan-2-amine **4.13n** (150 mg, 1.1 mmol, 1 equiv), Et_3N (0.170 mL, 1.21 mmol, 1.2 equiv) and triphosgene (102 mg, 0.343 mmol, 0.34 equiv) were reacted in dry benzene (5 mL) at 0 °C. The desired Benzyl(isopropyl)carbamoyl chloride **4.11n** was obtained as a yellowish solid (64 mg, 0.33 mmol, 30 %) and used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 – 7.27 (m, 5H), 4.67 (s, 2H), 4.30 – 4.20 (m, 1H), 1.20 (d, *J* = 6.8 Hz, 6H).

Isopropyl(phenethyl)carbamoyl chloride 4.11o

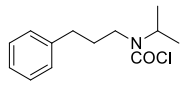


Chemical Formula: $C_{12}H_{16}ClNO$

Following general procedure **carbamoyl chloride**, *N*-phenethylpropan-2-amine **4.13o** (400 mg, 2.45 mmol, 1 equiv), Et_3N (0.413 mL, 2.94 mmol, 1.2 equiv) and triphosgene (247 mg, 0.833 mmol, 0.34 equiv) were reacted in dry benzene (15 mL) at 0 °C. The desired Isopropyl(phenethyl)carbamoyl chloride **4.11o** was obtained as a yellowish solid (515 mg, 2.28 mmol, 93 %) and used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.37 – 7.18 (m, 5H), 4.61 – 4.27 (m, 1H), 3.55 – 3.37 (m, 2H), 3.02 – 2.89 (m, 2H), 1.29 – 1.18 (m, 6H).

Isopropyl(3-phenylpropyl)carbamoyl chloride 4.11p

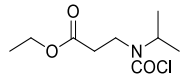


Chemical Formula: $C_{13}H_{18}ClNO$

Following general procedure **carbamoyl chloride**, *N*-isopropyl-3-phenylpropan-1-amine **4.13p** (302 mg, 0.916 mmol, 1 eq), Et_3N (0.154 mL, 1.1 mmol, 1.2 equiv) and triphosgene (96 mg, 0.311 mmol, 0.34 equiv) were reacted in dry benzene (4.8 mL) at 0 °C. The desired Isopropyl(3-phenylpropyl)carbamoylchloride **4.11p** was obtained as a brownish solid (298 mg, 0.76 mmol, 83 %) and used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33 – 7.27 (m, 2H), 7.25 – 7.16 (m, 3H), 4.56 – 4.16 (m 1H), 3.35 – 3.09 (m, 2H), 2.71 – 2.49 (m, 2H), 2.08 – 1.87 (m, 2H), 1.22 – 1.14 (m, 6H).

Ethyl 3-((chlorocarbonyl)(isopropyl)amino)propanoate 4.11q

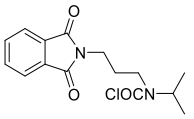


Chemical Formula: $C_9H_{16}ClNO_3$

Following general procedure **carbamoyl chloride**, ethyl 3-(isopropylamino)propanoate **4.13q** (400 mg, 2.52 mmol, 1 equiv), Et_3N (0.425 mL, 3.02 mmol, 1.2 equiv) and triphosgene (254 mg, 0.857 mmol, 0.34 equiv) were reacted in dry benzene (15 mL) at 0 °C . The desired Ethyl 3-((chlorocarbonyl)(isopropyl)amino)propanoate **4.11q** was obtained as an orange oil (465 mg, 2.09 mmol, 83 %) and used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.60 – 4.26 (m, 1H), 4.21 – 4.11 (m, 2H), 3.67 – 3.49 (m, 2H), 2.74 – 2.62 (m, 2H), 1.32 – 1.21 (m, 9H).

(3-(1,3-*di*oxoisoindolin-2-yl)propyl)(isopropyl)carbamoyl chloride 4.11r

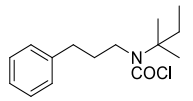


Chemical Formula: $C_{15}H_{17}ClN_2O_3$

Following general procedure **carbamoyl chloride**, 2-(3-(isopropylamino)propyl)isoindoline-1,3-dione **4.13r** (300 mg, 1.22 mmol 1 equiv), Et_3N (0.206 mL, 1.46 mmol, 1.2 equiv) and triphosgene (123 mg, 0.415 mmol, 0.34 equiv) were reacted in dry benzene (6.2 mL) at 0 °C . The desired (3-(1,3-dioxoisoindolin-2-yl)propyl)(isopropyl)carbamoyl chloride **4.11r** was obtained as a yellowish solid (302 mg, 1.0 mmol, 82 %) and used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.08 – 7.67 (m, 4H), 4.57 – 4.17 (m, 1H), 3.77 – 3.69 (m, 2H), 3.54 – 3.26 (m, 2H), 2.08 – 2.00 (m, 2H), 1.28 – 1.22 (m, 6H).

***Tert*-pentyl(3-phenylpropyl)carbamoyl chloride 4.11s**

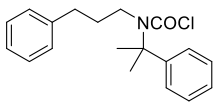


Chemical Formula: $C_{15}H_{22}ClNO$

Following general procedure **carbamoyl chloride**, 2-methyl-N-(3-phenylpropyl)butan-2-amine **4.13s** (400 mg, 1.95 mmol, 1 equiv), Et_3N (0.329 mL, 2.34 mmol, 1.2 equiv) and triphosgene (197 mg, 0.663 mmol, 0.34 equiv) were reacted in dry benzene (5 mL, 0.4M) at 0 °C . The desired Tert-pentyl(3-phenylpropyl)carbamoyl chloride **4.11s** was obtained as a yellowish oil (400 mg, 1.53 mmol, 77 %) and used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33 – 7.17 (m, 5H), 3.45 (t, *J* = 8.4 Hz, 2H), 2.61 (t, *J* = 7.6 Hz, 2H), 2.03 – 1.93 (m, 2H), 1.83 (q, *J* = 7.5 Hz, 2H), 1.34 (s, 6H), 0.80 (t, *J* = 7.5 Hz, 3H).

(2-phenylpropan-2-yl)(3-phenylpropyl)carbamoyl chloride 4.11t

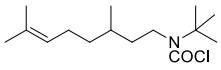


Chemical Formula: $C_{19}H_{22}ClNO$

Following general procedure **carbamoyl chloride**, 3-phenyl-*N*-(2-phenylpropan-2-yl)propan-1-amine **4.13t** (250 mg, 0.987 mmol 1 equiv), Et_3N (0.166 mL, 1.18 mmol, 1.2 equiv) and triphosgene (100 mg, 0.336 mmol, 0.34 equiv) were reacted in dry benzene (5 mL) at 0 °C . The desired (2-phenylpropan-2-yl)(3-phenylpropyl)carbamoyl chloride **4.11t** was obtained as a white solid (290 mg, 0.91 mmol, 92 %) and used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34 – 7.26 (m, 5H), 7.25 – 7.18 (m, 5H), 3.65 – 3.58 (m, 1H), 2.65 (t, *J* = 7.6 Hz, 2H), 2.19 – 2.11 (m, 2H), 1.68 (s, 6H).

***Tert*-butyl(3,7-*d*imethyloct-6-en-1-yl)carbamoyl chloride 4.11u**

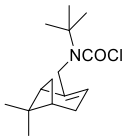


Chemical Formula: $C_{15}H_{28}ClNO$

Following general procedure **carbamoyl chloride**, *N*-(tert-butyl)-3,7-dimethyloct-6-en-1-amine **4.13u** (400 mg, 1.89 mmol, 1 equiv), Et_3N (0.319 mL, 2.27 mmol, 1.2 equiv) and triphosgene (191 mg, 0.643 mmol, 0.34 equiv) were reacted in dry benzene (11.2 mL, 0.4M) at 0 °C. The desired Tert-butyl(3,7-dimethyloct-6-en-1-yl)carbamoyl chloride **4.11u** was obtained as a yellowish solid (404 mg, 1.47 mmol, 78 %) and used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.07 (dtd, *J* = 7.1, 3.5, 2.7, 1.4 Hz, 1H), 3.59 – 3.40 (m, 2H), 1.99 (dq, *J* = 14.3, 7.3 Hz, 2H), 1.68 (d, *J* = 1.4 Hz, 3H), 1.71 – 1.62 (m, 1H), 1.60 (s, 3H), 1.45 (s, 9H), 1.38 – 1.13 (m, 3H) 0.92 (d, *J* = 6.4 Hz, 3H).

***Tert*-butyl(((1*S*,5*R*)-6,6-*d*imethylbicyclo[3.1.1]hept-2-en-3-yl)methyl)carbamoyl chloride 4.11v**

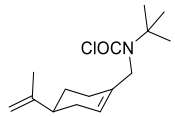


Chemical Formula: $C_{15}H_{24}ClNO$

Following general procedure **carbamoyl chloride**, dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl)-2-methylpropan-2-amine **4.13v** (280 mg, 1.35 mmol, 1 equiv), Et_3N (0.228 mL, 1.62 mmol, 1.2 equiv) and triphosgene (136 mg, 0.459 mmol, 0.34 equiv) were reacted in dry benzene (7 mL) at 0 °C . The desired Tert-butyl(((1*S*,5*R*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-3-yl)methyl)carbamoyl chloride **4.11v** was obtained as a yellowish solid (270 mg, 1.0 mmol, 74 %) and used without further purification

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.39 – 5.35 (m, 1H), 4.12 – 3.92 (m, 2H), 2.44 – 2.21 (m, 4H), 2.13 (dtd, *J* = 5.8, 2.9, 1.3 Hz, 1H), 1.95 (td, *J* = 5.6, 1.6 Hz, 1H), 1.46 (s, 9H), 1.29 (s, 3H), 0.86 (s, 3H).

(*S*)-*tert*-butyl((4-(prop-1-en-2-yl)cyclohex-1-en-1-yl)methyl)carbamoyl chloride 4.11w

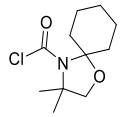


Chemical Formula: $C_{15}H_{24}ClNO$

Following general procedure **carbamoyl chloride**, (*S*)-2-methyl-*N*-((4-(prop-1-en-2-yl)cyclohex-1-en-1-yl)methyl)propan-2-amine **4.13w** (259 mg, 1.25 mmol 1 equiv), Et_3N (0.211 mL, 1.5 mmol, 1.2 equiv) and triphosgene (126 mg, 0.425 mmol, 0.34 equiv) were reacted in dry benzene (7.2 mL) at 0 °C .The desired (*S*)-tert-butyl((4-(prop-1-en-2-yl)cyclohex-1-en-1-yl)methyl)carbamoyl chloride **4.11w** was obtained as a reddish oil (300 mg, 1.11 mol, 89 %) and used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.61 – 5.58 (m, 1H), 4.76 – 4.65 (m, 2H), 4.15 – 3.94 (m, 2H), 2.23 – 2.11 (m, 2H), 2.07 – 1.81 (m, 2H), 1.74 (s, 3H), 1.44 (s, 9H).

3,3-*d*imethyl-1-oxa-4-azaspiro[4.5]decane-4-carbamoyl chloride 4.11x

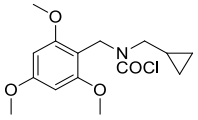


Chemical Formula: $C_{11}H_{18}ClNO_2$

Following general procedure **carbamoyl chloride**, 3,3-dimethyl-1-oxa-4-azaspiro[4.5]decane **4.11x** (1 g, 5.91 mmol, 1 equiv), Et_3N (0.997 mL, 7.10 mmol, 1.2 equiv) and triphosgene (596 mg, 2.01 mmol, 0.34 equiv) were reacted in dry benzene (30 mL) at 0 °C . The desired 3,3-dimethyl-1-oxa-4-azaspiro[4.5]decane-4-carbamoyl chloride **4.11x** was obtained as a yellowish solid (1.29 g, 5.55 mmol, 94 %) and used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.79 – 3.71 (m, 2H), 2.57 – 2.29 (m, 2H), 1.73 – 1.55 (m, 7H), 1.53 – 1.44 (m, 6H), 1.27 – 1.15 (m, 1H).

(cyclopropylmethyl)(2,4,6-trimethoxybenzyl)carbamoyl chloride 4.11y

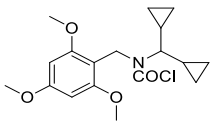


Chemical Formula: $C_{15}H_{20}ClNO_4$

Following general procedure **carbamoyl chloride**, 1-cyclopropyl-*N*-(2,4,6-trimethoxybenzyl)methanamine **4.13y** (400 mg, 1.59 mmol, 1 equiv), Et_3N (0.268 mL, 1.91 mmol, 1.2 equiv) and triphosgene (161 mg, 0.541 mmol, 0.34 equiv) were reacted in dry benzene (8 mL) at 0 °C. The desired (cyclopropylmethyl)(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11y** was obtained as a yellowish solid (428 mg, 1.36 mmol, 83 %) and used without further purification.

^{1}H NMR (250 MHz, $CDCl_3$) δ = 6.10 (s, 2H), 4.78 (s, 1H), 4.69 (s, 1H), 3.81 – 3.78 (m, 9H), 3.05 (dd, *J* = 18.5, 7.2 Hz, 2H), 1.26 – 1.16 (m, 1H), 0.55 – 0.32 (m, 2H), 0.29 – 0.12 (m, 2H).

(dicyclopropylmethyl)(2,4,6-trimethoxybenzyl)carbamoyl chloride 4.11z



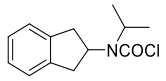
Chemical Formula: $C_{18}H_{24}ClNO_4$

Following general procedure **carbamoyl chloride**, 1,1-dicyclopropyl-*N*-(2,4,6-trimethoxybenzyl)methanamine **4.13z** (300 mg, 1.03 mmol, 1 equiv), Et_3N (0.174 mL, 1.24 mmol, 1.2 equiv) and triphosgene (104 mg, 0.350 mmol, 0.34 equiv) were reacted in dry benzene (6 mL) at 0 °C . The desired (dicyclopropylmethyl)(2,4,6-trimethoxybenzyl)carbamoyl

chloride **4.11z** was obtained as a yellowish solid (287 mg, 0.81mmol, 79 %) and used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.09 (s, 2H), 4.80 (s, 2H), 3.82 (s, 3H), 3.79 (s, 6H), 1.31 – 1.18(m, 1H), 0.57 – 0.41 (m, 4H), 0.26 – 0.18 (m, 4H), -0.07 – -0.21 (m, 2H).

(2,3-*d*ihydro-1H-inden-2-yl)(isopropyl)carbamoyl chloride 4.11aa

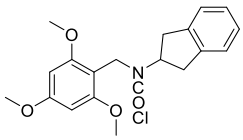


Chemical Formula: $C_{13}H_{16}ClNO$

Following general procedure **carbamoyl chloride**, *N*-isopropyl-2,3-dihydro-1H-inden-2-amine **4.13aa** (150 mg, 0.856 mmol 1 equiv), Et_3N (0.144 mL, 1.03 mmol, 1.2 equiv) and triphosgene (86 mg, 0.291 mmol, 0.34 equiv) were reacted in dry benzene (4.2 mL) at 0 °C. The desired (2,3-dihydro-1H-inden-2-yl)(isopropyl)carbamoyl chloride **4.11aa** was obtained as a yellowish oil (160 mg, 0.67 mmol, 78 %) and used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.23 – 7.14 (m, 4H), 5.23 – 4.60 (m, 1H), 4.22 – 3.71 (m, 1H), 3.69 – 3.38 (m, 2H), 3.31 – 2.88 (m, 2H), 1.26 – 1.40 (m, 6H).

(2,3-dihydro-1H-inden-2-yl)(2,4,6-trimethoxybenzyl)carbamoyl chloride 4.11ab

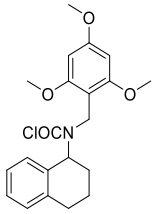


Chemical Formula: $C_{20}H_{22}ClNO_4$

Following general procedure **carbamoyl chloride**, *N*-(2,4,6-trimethoxybenzyl)-2,3-dihydro-1H-inden-2-amine **4.13ab** (269 mg, 0.858 mmol 1 equiv), Et_3N (0.144 mL, 1.03 mmol, 1.2 equiv) and triphosgene (86 mg, 0.291 mmol, 0.34 equiv) were reacted in dry benzene (4.2 mL) at 0 °C. The desired (2,3-dihydro-1H-inden-2-yl)(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11ab** was obtained as a white solid (290 mg, 0.77 mmol, 90 %) and used without further purification.

^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.07 (s, 4H), 6.10 (s, 2H), 4.83 (s, 2H), 4.15 – 3.99 (m, 1H), 3.82 (s, 3H), 3.80 (s, 6H), 3.49 – 3.33 (m, 2H), 2.74 – 2.59 (m, 2H).

(1,2,3,4-tetrahydronaphthalen-1-yl)(2,4,6-trimethoxybenzyl)carbamoyl chloride 4.11ac

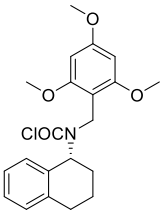


Chemical Formula: $C_{21}H_{24}ClNO_4$

Following general procedure **carbamoyl chloride**, *N*-(2,4,6-trimethoxybenzyl)-1,2,3,4-tetrahydronaphthalen-1-amine **4.13ac** (490 mg, 1.50 mmol, 1 equiv), Et_3N (0.253 mL, 1.80 mmol, 1.2 equiv) and triphosgene (151 mg, 0.510 mmol, 0.34 equiv) were reacted in dry benzene (7.4 mL) at 0 °C. The desired (1,2,3,4-tetrahydronaphthalen-1-yl)(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11ac** was obtained as a yellowish solid (480 mg, 1.23 mmol, 82 %) and used without further purification.

^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.09 – 6.97 (m, 4H), 6.10 – 6.03 (m 2H), 5.03 – 4.83 (m, 2H), 4.71 – 4.50 (m, 1H), 3.81 (s, 3H), 3.80 (s, 6H), 3.80 – 3.73 (m, 2H), 2.86 – 2.50 (m, 2H), 1.97 – 1.66 (m, 2H).

(*R*)-(1,2,3,4-tetrahydronaphthalen-1-yl)(2,4,6-trimethoxybenzyl)carbamoyl chloride (-)-4.11ac

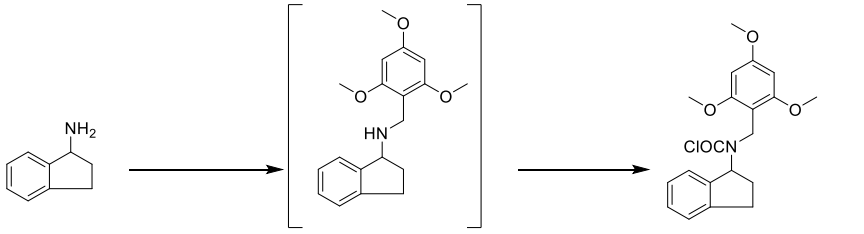


Chemical Formula: $C_{21}H_{24}ClNO_4$

Following general procedure **carbamoyl chloride**, (*R*)-*N*-(2,4,6-trimethoxybenzyl)-1,2,3,4-tetrahydronaphthalen-1-amine **(-)-4.13ac** (600 mg, 1.83 mmol, 1 equiv), Et_3N (0.308 mL, 2.20 mmol, 1.2 equiv) and triphosgene (185 mg, 0.622 mmol, 0.34 equiv) were reacted in dry benzene (10 mL) at 0 °C. The desired (*R*)-(1,2,3,4-tetrahydronaphthalen-1-yl)(2,4,6-trimethoxybenzyl)carbamoyl chloride **(-)-4.11ac** was obtained as a yellowish solid (613 mg, 1.53 mmol, 86 %) and used without further purification.

^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.09 – 6.95 (m, 4H), 6.10 – 6.03 (m, 2H), 5.03 – 4.82 (m, 2H), 4.71 – 4.49 (m, 1H), 3.81 (s, 3H), 3.80 (s, 6H), 3.79 – 3.73 (m, 2H), 2.87 – 2.52 (m, 2H), 1.99 – 1.67 (m, 2H).

(2,3-dihydro-1H-inden-1-yl)(2,4,6-trimethoxybenzyl)carbamoyl chloride 4.11ad



Chemical Formula: $C_{20}H_{22}ClNO_4$

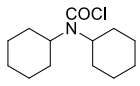
76 %

Following general procedure **B** for the synthesis of amines, 2,3-dihydro-1H-inden-1-amine (200 mg, 1.5 mmol, 1 equiv), 2,4,6-trimethoxybenzaldehyde (294 mg, 1.5 mmol, 1 equiv), and AcOH (0.172 mL, 3 mmol 2 equiv) were stirred at room temperature in DCE (15 mL) for 30 minutes. $NaBH(OAc)_3$ (636 mg, 3 mmol, 2 equiv) was then added to the turning solution, which was reacted overnight. Then, the mixture was quenched using a solution of NaOH (1M) and the crude was stirred for further 30 minutes. The crude was extracted twice with DCM, dried over sodium sulfate, filtered and evaporated under vacuum.

Following general procedure **carbamoyl chloride**, *N*-(2,4,6-trimethoxybenzyl)-2,3-dihydro-1H-inden-1-amine (470 mg, 1.50 mmol, 1 equiv), Et_3N (0.632 mL, 4.50 mmol, 1.2 equiv) and triphosgene (151 mg, 0.51 mmol, 0.34 equiv) were reacted in dry benzene (7.6 mL) at 0 °C. The desired (2,3-dihydro-1H-inden-1-yl)(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11ad** was obtained as a yellowish solid (430 mg, 1.14 mmol, 76 %) and used without further purification.

^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.29 – 6.96 (m 4H), 6.11 – 5.93 (m, 2H), 5.07 – 4.75 (m, 2H), 3.85 – 3.75 (m, 9H), 3.70 – 3.61 (m, 2H), 3.51 – 3.40 (m, 1H), 3.14 – 3.05 (m, 1H), 2.19 – 2.01 (m, 1H).

Dicyclohexylcarbamoyl chloride 4.11ae

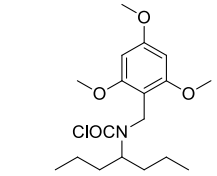


Chemical Formula: $C_{13}H_{22}ClNO$

Following general procedure **carbamoyl chloride**, dicyclohexylamine (363 mg, 2.0 mmol 1 equiv), Et_3N (0.337 mL, 2.24 mmol, 1.2 equiv) and triphosgene (202 mg, 0.68 mmol, 0.34 equiv) were reacted in dry benzene (10 mL) at 0 °C. The desired Dicyclohexylcarbamoyl chloride **4.11ae** was obtained as a yellowish solid (450 mg, 1.84 mmol, 92 %) and used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.12 (s, 1H), 3.10 (s, 1H), 2.19 (s, 2H), 1.85 – 1.80 (m, 6H), 1.65 – 1.54 (m, 2H), 1.54 – 1.04 (m, 10H).

Pentan-3-yl(2,4,6-trimethoxybenzyl)carbamoyl chloride 4.11af



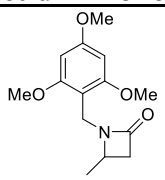
Chemical Formula: $C_{18}H_{28}ClNO_4$

Following general procedure carbamoyl chlorides, N-(2,4,6-trimethoxybenzyl)pentan-3-amine(400 mg, 1.5mmol 1 equiv), Et3N (0.250mL, 1.8mmol, 1.2 equiv) and triphosgene (151mg, 0.51mmol, 0.34 equiv) were reacted in dry benzene (7 mL) at 0 °C. The desired Pentan-3-yl(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11af** was obtained as a yellowish solid (430 mg, 1.30 mmol, 87%) and used without further purification.

^{1}H NMR (250 MHz, $CDCl_3$) δ = 6.16 –6.06 (m, 2H), 4.75 –4.60 (m, 2H), 3.88 –3.78 (m,9H), 3.10–2.93 (m, 1H), 1.89 –1.64 (m, 2H), 1.54 –1.33 (m, 2H), 0.96 –0.52 (m, 6H).

3.9. β-lactams's synthesis

4-methyl-1-(2,4,6-trimethoxybenzyl)azetidin-2-one 4.12a



Chemical Formula: $C_{14}H_{19}NO_4$
Exact Mass: 265.1314

Standard scale synthesis: Conditions A: Double-chamber system:

Following general procedure **A**, Chamber A was filled with $Pd(OAc)_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(*t*-Bu)$_3$●HBF_4 (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy_2NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with isopropyl(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11a** (40 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing 4-methyl-1-(2,4,6-trimethoxybenzyl)azetidin-2-one **4.12a** (32.5 mg, 0.122 mmol, 92 %).

Standard scale synthesis: Conditions B: CO atmosphere

Following general procedure **B**, isopropyl(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11a** (40 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C, the excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing 4-methyl-1-(2,4,6-trimethoxybenzyl)azetidin-2-one **4.12a** (30.0 mg, 0.064 mmol, 85 %).

Enantioselective conditions: CO atmosphere

Following general procedure **B**, Isopropyl(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11a** (400 mg, 1.33 mmol, 1 equiv) was reacted with $PdCl_2$ (24 mg, 0.133 mmol, 10 mol%), **L** ligand (332 mg , 0.266 mmol, 20 mol%), pivalic acid (41 mg, 0.4 mmol, 30 mol%) and cesium carbonate (650 mg, 2 mmol, 1.5 equiv) in mesitylene (26.2 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C, the excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing (*R*)-4-methyl-1-(2,4,6-trimethoxybenzyl)azetidin-2-one **4.12a** (266 mg, 1 mmol, 75 %, e.r.: 92:8). **Optical rotation :** $[\alpha]_D^{20} = +71.8°$ (c = 1.0, $CHCl_3$)

Enantioselective conditions: Double-chamber system:

Following general procedure **A**, Chamber A was filled with $Pd(OAc)_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(*t*-Bu)$_3$●HBF_4 (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy_2NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with isopropyl(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11a** (40 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), **L** ligand (33.2 mg , 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (65 mg, 0.2 mmol, 1.5 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing (*R*)-4-methyl-1-(2,4,6-trimethoxybenzyl)azetidin-2-one **4.12a** (30.5 mg, 0.114 mmol, 86 %, e.r.: 86:14).

Tenfold scale synthesis:

Conditions A: Double-chamber system:

Following general procedure **A**, Chamber A was filled with $Pd(OAc)_2$ (89 mg, 0.4 mmol, 30 mol%), P(*t*-Bu)$_3$●HBF_4 (120 mg, 0.4 mmol, 30 mol%), COgen (970 mg, 4 mmol, 3.0 equiv), Cy_2NMe (1.610 g, 7.98 mmol, 6.0 equiv) and mesitylene (5 mL). Chamber B, previously charged with isopropyl(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11a** (400 mg, 1.33 mmol, 1 equiv) was reacted with $PdCl_2$ (24 mg, 0.133 mmol, 10 mol%), cataCXium AHI (120 mg , 0.266 mmol, 20 mol%), pivalic acid (41 mg, 0.4 mmol, 30 mol%) and cesium carbonate (1.30 g, 4 mmol, 3.0 equiv) in mesitylene (26.2 mL). The two chambers system was reacted for 18h at 120 °C. The excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing 4-methyl-1-(2,4,6-trimethoxybenzyl)azetidin-2-one **4.12a** (337 mg, 1.26 mmol, 95 %).

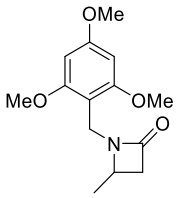
Conditions A: Double-chamber system: Under air atmosphere:

Following general procedure **A**, Chamber A was filled with $Pd(OAc)_2$ (89 mg, 0.4 mmol, 30 mol%), P(*t*-Bu)$_3$●HBF_4 (120 mg, 0.4 mmol, 30 mol%), COgen (970 mg, 4 mmol, 3.0 equiv), Cy_2NMe (1.610 g, 7.98 mmol, 6.0 equiv) and mesitylene (commercial batch under argon atmosphere) (5 mL). Chamber B, previously charged with isopropyl(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11a** (400 mg, 1.33 mmol, 1 equiv) was reacted with $PdCl_2$ (24 mg, 0.133 mmol, 10 mol%), cataCXium AHI (120 mg , 0.266 mmol, 20 mol%), pivalic acid (41 mg, 0.4 mmol, 30 mol%) and cesium carbonate (1.30 g, 4 mmol, 3.0 equiv) in mesitylene (commercial batch under argon atmosphere) (26.2 mL). The two chambers system was reacted for 18h at 120 °C under air atmosphere. The excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing 4-methyl-1-(2,4,6-trimethoxybenzyl)azetidin-2-one **4.12a** (266 mg, 1.0 mmol, 75 %).

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 6.11 (s, 2H), 4.57 (d, *J* = 13.9 Hz, 1H), 4.13 (dd, *J* = 13.8, 1.1 Hz, 1H), 3.81 (s, 9H), 3.41 – 3.33 (m, 1H), 2.90 (dd, *J* = 14.2, 4.9 Hz, 1H), 2.38 (ddd, *J* = 14.2, 2.2, 1.0 Hz, 1H), 1.17 (d, *J* = 6.0 Hz, 3H). **^{13}C NMR ($CDCl_3$, 101 MHz) :** δ = 166.5, 161.2, 159.7, 104.6, 90.3, 55.8, 55.5, 47.0, 43.8, 32.4, 18.7. **IR (neat):** ν = 2946, 1739, 1600, 1140cm^{-1}. **HRMS (ESI):** Calculated for $C_{14}H_{19}NNaO_4$ ($[M+Na]^+$): 288.1206; found: 288.1208

SHIMADZU LabSolutions

Analysis Report



Chemical Formula: $C_{14}H_{19}NO_4$
Exact Mass: 265.1314
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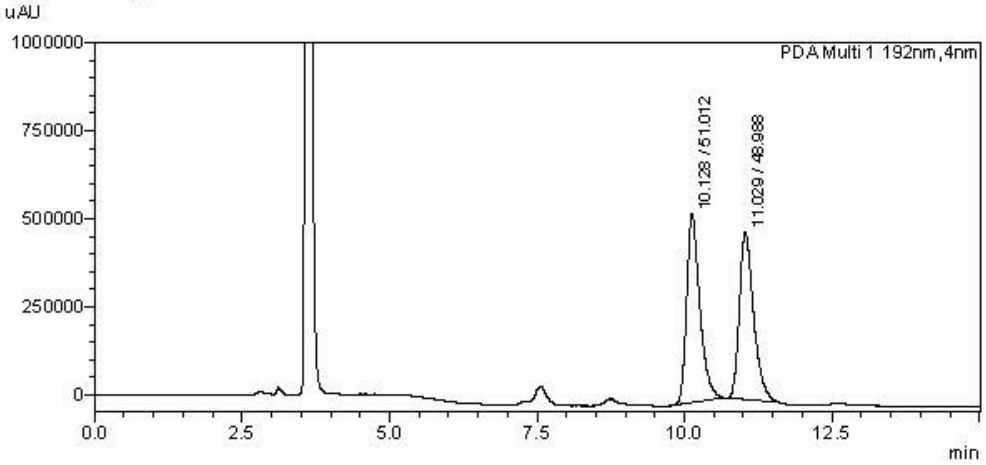

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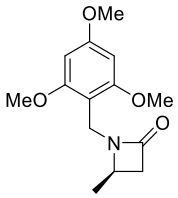
D:\Data\David D\rr0792-run-col3-IA002.lcd

SHIMADZU LabSolutions

Analysis Report



Chemical Formula: $C_{14}H_{19}NO_4$
Exact Mass: 265.1314
(+)-4.12a

<Sample Information>

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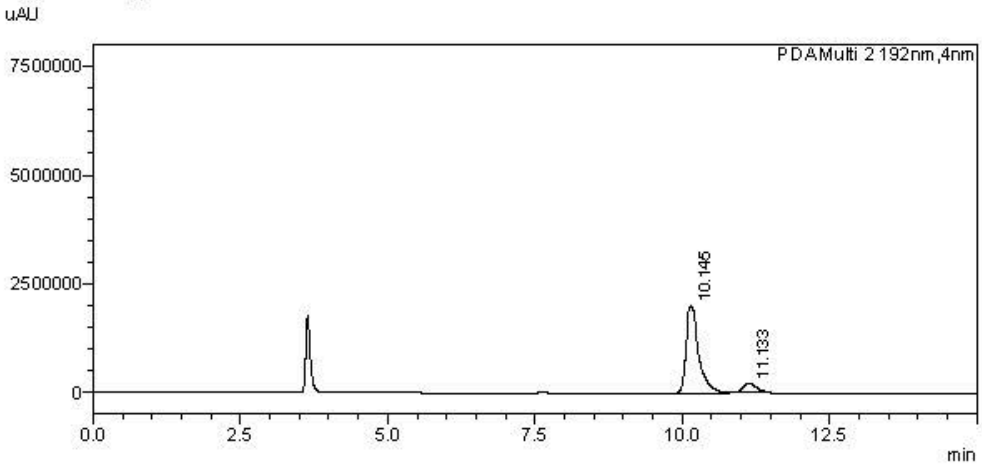

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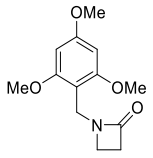
Name

D:\Data\David D\scaleup-run-col3-IA.lcd

1-(2,4,6-trimethoxybenzyl)azetidin-2-one 4.12b



Chemical Formula: $C_{13}H_{17}NO_4$
Exact Mass: 251.1158

Conditions A: Double-chamber system:

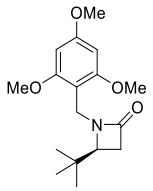
Following general procedure **A**, Chamber A was filled with $Pd(OAc)_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(*t*-Bu)$_3$●HBF_4 (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy_2NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with ethyl(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11b** (38.3 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing 1-(2,4,6-trimethoxybenzyl)azetidin-2-one **4.12b** (16.0 mg, 0.064 mmol, 48 %).

Conditions B: CO atmosphere

Following general procedure **B**, ethyl(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11b** (38.3 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C, the excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing 1-(2,4,6-trimethoxybenzyl)azetidin-2-one **4.12b** (11.4 mg, 0.045 mmol, 34 %).

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 6.12 (s, 2H), 4.38 (s, 2H), 3.82 (s, 3H), 3.81 (s, 6H), 3.01 (t, *J* = 4.0 Hz, 2H), 2.79 (t, *J* = 4.0 Hz, 2H). **^{13}C NMR ($CDCl_3$, 101 MHz) :** δ = 167.2, 161.2, 159.7, 104.2, 90.4, 55.9, 55.5, 38.7, 36.2, 34.1. **IR (neat):** ν = 2939, 1737, 1596, 1145, 814 cm^{-1}. **HRMS (ESI):** Calculated for $C_{13}H_{17}NNaO_4$ ($[M+Na]^+$): 274.1050; found: 274.1051

(*S*)-4-(*tert*-butyl)-1-(2,4,6-trimethoxybenzyl)azetidin-2-one 4.12e



Chemical Formula: $C_{17}H_{25}NO_4$
Exact Mass: 307.1784

Conditions A: Double-chamber system:

Following general procedure **A**, Chamber A was filled with $Pd(OAc)_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(*t*-Bu)$_3$●HBF_4 (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy_2NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with (S)-(3,3-dimethylbutan-2-yl)(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11e** (47.6 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing (*S*)-4-(tert-butyl)-1-(2,4,6-trimethoxybenzyl)azetidin-2-one **4.12e** (30.7 mg, 0.100 mmol, 75 %).

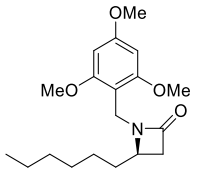
Conditions B: CO atmosphere

Following general procedure **B**, (*S*)-(3,3-dimethylbutan-2-yl)(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11e** (47.6 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C, the excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing (*S*)-4-(tert-butyl)-1-(2,4,6-trimethoxybenzyl)azetidin-2-one **4.12e** (15.5 mg, 0.051 mmol, 38 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.10 (s, 2H), 4.64 (d, *J* = 14.5 Hz, 1H), 4.21 (d, *J* = 14.5 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 6H), 2.97 (dd, *J* = 5.4, 2.6 Hz, 1H), 2.65 (dd, *J* = 14.6, 5.4 Hz, 1H), 2.57 – 2.50 (m, 1H), 0.82 (s, 9H). **^{13}C NMR ($CDCl_3$, 101 MHz):** δ = 169.0, 161.0, 159.6, 103.8, 90.3, 59.9, 55.7, 55.4, 37.8, 35.3, 32.4, 25.7. **IR (neat):** ν = 2975, 1739, 743 cm^{-1}.

HRMS (ESI): Calculated for $C_{17}H_{26}NO_4$ ($[M+H]^+$): 308.1856; found: 308.1859 **Optical rotation :** $[\alpha]_D^{20} = +50.1°$ (c = 0.7, $CHCl_3$)

(*R*)-4-hexyl-1-(2,4,6-trimethoxybenzyl)azetidin-2-one 4.12f



Chemical Formula: $C_{19}H_{29}NO_4$
Exact Mass: 335.2097

Conditions A: Double-chamber system:

Following general procedure **A**, Chamber A was filled with $Pd(OAc)_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(*t*-Bu)$_3$●HBF_4 (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy_2NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with (S)-octan-2-yl(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11f** (49.5 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing (*R*)-4-hexyl-1-(2,4,6-trimethoxybenzyl)azetidin-2-one **4.12f** (41 mg, 0.122 mmol, 92 %).

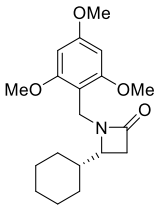
Conditions B: CO atmosphere

Following general procedure **B**, (*S*)-octan-2-yl(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11f** (49.5 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C, the excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing (*R*)-4-hexyl-1-(2,4,6-trimethoxybenzyl)azetidin-2-one **4.12f** (39.3 mg, 0.117 mmol, 88 %).

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 6.10 (s, 2H), 4.56 (d, *J* = 14.0 Hz, 1H), 4.13 (d, *J* = 13.9 Hz, 1H), 3.81 – 3.78 (m, 9H), 3.26 – 3.20 (m, 1H), 2.81 (dd, *J* = 14.2, 5.0 Hz, 1H), 2.45 – 2.39 (m, 1H), 1.80 – 1.69 (m, 1H), 1.28 – 1.18 (m, 9H), 0.86 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 101 MHz) : δ = 166.9, 161.2, 159.6, 104.5, 90.3, 55.8, 55.4, 51.2, 41.8, 32.7, 32.5, 31.8, 29.3, 25.0, 22.7, 14.2. **IR (neat):** ν = 2962, 1739, 1608, 1140, 732 cm^{-1}. **HRMS (ESI):** Calculated for $C_{19}H_{30}NO_4$ ($[M+H]^+$): 336.2169; found: 336.2167 **Optical rotation :** $[\alpha]_D^{20}$ = +46.6° (c = 1.3, $CHCl_3$)

(*S*)-4-cyclohexyl-1-(2,4,6-trimethoxybenzyl)azetidin-2-one 4.12g



Chemical Formula: $C_{19}H_{27}NO_4$
Exact Mass: 333.1940

Conditions A: Double-chamber system:

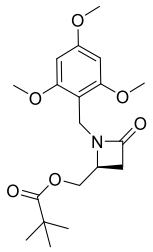
Following general procedure **A**, Chamber A was filled with $Pd(OAc)_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(*t*-Bu)$_3$●HBF_4 (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy_2NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with (S)-(1-cyclohexylethyl)(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11g** (49.2 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing (*S*)-4-cyclohexyl-1-(2,4,6-trimethoxybenzyl)azetidin-2-one **4.12g** (44.4 mg, 0.133 mmol, 100 %).

Conditions B: CO atmosphere

Following general procedure **B**, (*S*)-(1-cyclohexylethyl)(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11g** (49.2 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C, the excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing (*S*)-4-cyclohexyl-1-(2,4,6-trimethoxybenzyl)azetidin-2-one **4.12g** (39.1 mg, 0.117 mmol, 88 %).

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 6.09 (s, 2H), 4.57 (d, *J* = 14.0 Hz, 1H), 4.16 (d, *J* = 14.0 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 6H), 3.13 – 3.08 (m, 1H), 2.65 (dd, *J* = 14.3, 5.1 Hz, 1H), 2.53 (d, *J* = 14.3 Hz, 1H), 1.70 – 1.46 (m, 5H), 1.19 – 1.04 (m, 4H), 0.91 – 0.72 (m, 2H). **^{13}C NMR ($CDCl_3$, 101 MHz) :** δ = 167.7, 161.1, 159.6, 104.1, 90.3, 55.7, 55.4, 55.4, 39.2, 38.0, 33.7, 29.5, 26.5, 26.3, 26.3, 26.0. **IR (neat):** ν = 2972, 1729, 1628, 1120, 734 cm^{-1}. **HRMS (ESI):** Calculated for $C_{19}H_{28}NO_4$ ($[M+H]^+$): 334.2013; found: 334.2013 **Optical rotation :** $[\alpha]_D^{20}$ = -38.2° (c = 1.6, $CHCl_3$)

(*S*)-(4-oxo-1-(2,4,6-trimethoxybenzyl)azetidin-2-yl)methyl pivalate 4.12h



Chemical Formula: $C_{19}H_{27}NO_6$
Exact Mass: 365.1838

Conditions A: Double-chamber system:

Following general procedure **A**, Chamber A was filled with $Pd(OAc)_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(*t*-Bu)$_3$●HBF_4 (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy_2NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with (S)-2-((chlorocarbonyl)(2,4,6-trimethoxybenzyl)amino)propyl pivalate **4.11h** (53.5 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing (*S*)-(4-oxo-1-(2,4,6-trimethoxybenzyl)azetidin-2-yl)methyl pivalate **4.12h** (48.6 mg, 0.133 mmol, 100 %).

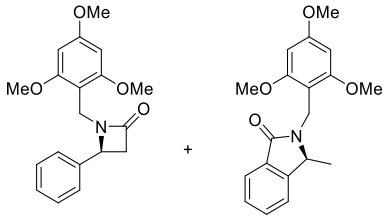
Conditions B: CO atmosphere

Following general procedure **B**, (*S*)-2-((chlorocarbonyl)(2,4,6-trimethoxybenzyl)amino)propyl pivalate **4.11h** (53.5 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C, the excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by

chromatography using cyclohexane/AcOEt as eluent, providing (*S*)-(4-oxo-1-(2,4,6-trimethoxybenzyl)azetidin-2-yl)methyl pivalate **4.12h** (42.7 mg, 0.117 mmol, 88 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.10 (s, 2H), 4.60 (d, *J* = 14.0 Hz, 1H), 4.25 (dd, *J* = 11.8, 4.3 Hz, 1H), 4.11 – 4.04 (m, 2H), 3.81 – 3.78 (m, 9H), 3.54 – 3.49 (m, 1H), 2.83 (dd, *J* = 14.3, 5.1 Hz, 1H), 2.70 (ddd, *J* = 14.2, 2.4, 1.0 Hz, 1H), 1.18 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$) δ =** 178.3, 166.2, 161.3, 159.5, 104.3, 90.4, 62.0, 55.8, 55.4, 49.4, 39.3, 39.1, 32.9, 27.2. **IR (neat):** ν = 1738, 1598, 904, 723cm^{-1}. **HRMS (ESI):** Calculated for $C_{19}H_{27}NNaO_6$ ($[M+Na]^+$): 388.1731; found: 388.1735 **Optical rotation :** $[\alpha]_D^{20}$ = +41.3° (c = 1.2, $CHCl_3$)

(*S*)-4-phenyl-1-(2,4,6-trimethoxybenzyl)azetidin-2-one 4.12i and (*S*)-3-methyl-2-(2,4,6-trimethoxybenzyl)isoindolin-1-one 4.12j



Conditions A: Double-chamber system:

Following general procedure **A**, Chamber A was filled with $Pd(OAc)_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(*t*-Bu)$_3$●HBF_4 (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy_2NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with (S)-(1-phenylethyl)(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11i** (48.4 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing (*S*)-4-phenyl-1-(2,4,6-trimethoxybenzyl)azetidin-2-one **4.12i** and (*S*)-3-methyl-2-(2,4,6-trimethoxybenzyl)isoindolin-1-one **4.12j** as an unseparable mixture (29.6 mg, 0.09 mmol, 68 %, 7/3).

Conditions B: CO atmosphere

Following general procedure **B**, (*S*)-(1-phenylethyl)(2,4,6-trimethoxybenzyl)carbamoyl chloride**4 11i** (48.4 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol,

30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C, the excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing (*S*)-4-phenyl-1-(2,4,6-trimethoxybenzyl)azetidin-2-one **4.12i** and (*S*)-3-methyl-2-(2,4,6-trimethoxybenzyl)isoindolin-1-one **4.12j** as an unseparable mixture (29.6 mg, 0.09 mmol, 68 %, 7/3).

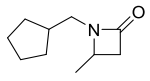
(*S*)-4-phenyl-1-(2,4,6-trimethoxybenzyl)azetidin-4.12i: Beta-lactam product :

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 – 7.22 (m, 3H), 7.22 – 7.16 (m, 2H), 5.99 (s, 2H), 4.67 (d, *J* = 13.8 Hz, 1H), 4.27 (dd, *J* = 5.3, 2.4 Hz, 1H), 4.11 (dd, *J* = 13.8, 1.1 Hz, 1H), 3.79 (s, 3H), 3.61 (s, 6H), 3.23 (dd, *J* = 14.4, 5.3 Hz, 1H), 2.72 (ddd, *J* = 14.4, 2.4, 1.0 Hz, 1H). **^{13}C NMR ($CDCl_3$, 101 MHz) :** δ = 167.2, 161.2, 159.5, 139.8, 130.9, 127.8, 126.2, 104.0, 90.1, 55.5, 55.4, 54.0, 46.7, 33.1. **IR (neat):** ν = 2950, 1737, 1680, 1595, 1150, 907, 727 cm^{-1}. **HRMS (ESI):** Calculated for $C_{19}H_{21}NNaO_4$ ($[M+Na]^+$): 350.1363; found: 350.1365

(*S*)-3-methyl-2-(2,4,6-trimethoxybenzyl)isoindolin-1-one 4.12j : Oxindole product :

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 7.86 (dt, *J* = 7.4, 1.1 Hz, 1H), 7.48 (td, *J* = 7.4, 1.3 Hz, 1H), 7.44 – 7.40 (m, 1H), 7.33 – 7.31 (m, 1H), 6.13 (s, 2H), 5.27 (d, *J* = 14.2 Hz, 1H), 4.44 (d, *J* = 14.1 Hz, 1H), 4.19 (q, *J* = 6.7 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 6H), 1.44 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR ($CDCl_3$, 101 MHz) :** δ = 167.3, 161.2, 160.0, 147.6, 132.5, 128.4, 127.7, 123.6, 121.8, 105.5, 90.4, 55.9, 55.5, 55.0, 32.5, 18.4.

1-(cyclopentylmethyl)-4-methylazetidin-2-one 4.12k



Chemical Formula: $C_{10}H_{17}NO$
Exact Mass: 167.1310

Conditions A: Double-chamber system:

Following general procedure **A**, Chamber A was filled with $Pd(OAc)_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(*t*-Bu)$_3$●HBF_4 (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy_2NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with (cyclopentylmethyl)(isopropyl)carbamoyl chloride **4.11k** (27.1 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL).

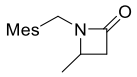
The two chambers system was reacted for 18h at 120 °C. The excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing 2k (16.7 mg, 0.100 mmol, 75 %).

Conditions B: CO atmosphere

Following general procedure **B**, (cyclopentylmethyl)(isopropyl)carbamoyl chloride **4.11k** (27.1 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C, the excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing 1-(cyclopentylmethyl)-4-methylazetidin-2-one **4.12k** (13.0 mg, 0.078 mmol, 59 %).

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 3.74 – 3.59 (m, 1H), 3.25 (dd, *J* = 13.9, 7.9 Hz, 1H), 3.04 (dd, *J* = 14.4, 4.8 Hz, 1H), 2.87 (dd, *J* = 14.0, 7.1 Hz, 1H), 2.47 (d, *J* = 14.4 Hz, 1H), 2.19 – 2.00 (m, 1H), 1.85 – 1.46 (m, 5H), 1.31 (d, *J* = 5.9 Hz, 3H), 1.26 – 1.14 (m, 3H). **^{13}C NMR ($CDCl_3$, 101 MHz) :** δ = 167.1, 47.7, 45.5, 44.0, 38.9, 30.9, 30.8, 25.5, 25.2, 18.8. **IR (neat):** ν = 2956, 1731, 907, 729 cm^{-1}. **HRMS (ESI):** Calculated for $C_{10}H_{17}NNaO$ ($[M+Na]^+$): 190.1202; found: 190.1202

4-methyl-1-(2,4,6-trimethylbenzyl)azetidin-2-one 4.12l



Chemical Formula: $C_{14}H_{19}NO$
Exact Mass: 217.1467

Conditions A: Double-chamber system:

Following general procedure **A**, Chamber A was filled with $Pd(OAc)_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(*t*-Bu)$_3$●HBF_4 (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy_2NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with isopropyl(2,4,6-trimethylbenzyl)carbamoyl chloride **4.11l** (33.8 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as

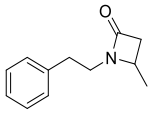
eluent, providing 4-methyl-1-(2,4,6-trimethylbenzyl)azetidin-2-one **4.12l** (20.2 mg, 0.093 mmol, 70 %).

Conditions B: CO atmosphere

Following general procedure **B**, isopropyl(2,4,6-trimethylbenzyl)carbamoyl chloride **4.11l** (33.8 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C, the excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing 4-methyl-1-(2,4,6-trimethylbenzyl)azetidin-2-one **4.12l** (19.4 mg, 0.078 mmol, 67 %).

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 6.85 (s, 2H), 4.48 (d, *J* = 14.7 Hz, 1H), 4.34 (d, *J* = 14.7 Hz, 1H), 3.48 – 3.38 (m, 1H), 3.01 (dd, *J* = 14.4, 5.0 Hz, 1H), 2.48 – 2.40 (m, 1H), 2.33 (s, 6H), 2.26 (s, 3H), 1.06 (d, *J* = 6.1 Hz, 3H). **^{13}C NMR ($CDCl_3$, 101 MHz) :** δ = 166.8, 137.6, 137.4, 129.4, 128.5, 47.6, 44.1, 38.9, 21.0, 20.1, 19.4. **IR (neat):** ν = 1733, 907, 731 cm^{-1}. **HRMS (ESI):** Calculated for $C_{14}H_{19}NNaO$ ($[M+Na]^+$): 240.1359; found: 240.1360

4-methyl-1-phenethylazetidin-2-one 4.12o



Chemical Formula: $C_{12}H_{15}NO$
Exact Mass: 189.1154

Conditions A: Double-chamber system:

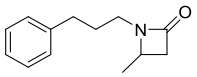
Following general procedure **A**, Chamber A was filled with $Pd(OAc)_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(*t*-Bu)$_3$●HBF_4 (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy_2NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with isopropyl(phenethyl)carbamoyl chloride **4.11o** (30.0 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing 4-methyl-1-phenethylazetidin-2-one **4.12o** (13.5 mg, 0.071 mmol, 54 %).

Conditions B: CO atmosphere

Following general procedure **B**, isopropyl(phenethyl)carbamoyl chloride **4.11o** (30.0 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C, the excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing 4-methyl-1-phenethylazetidin-2-one **4.12o** (7 mg, 0.037 mmol, 28 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.26 – 7.18 (m, 2H), 7.18 – 7.10 (m, 3H), 3.52 (dt, *J* = 14.6, 7.4 Hz, 1H), 3.46 – 3.39 (m, 1H), 3.15 (dt, *J* = 14.4, 7.4 Hz, 1H), 2.91 (dd, *J* = 14.4, 4.9 Hz, 1H), 2.80 (t, *J* = 7.4 Hz, 2H), 2.36 (dd, *J* = 14.4, 2.2 Hz, 1H), 1.11 (d, *J* = 6.2 Hz, 3H). **^{13}C NMR (101 MHz, $CDCl_3$) δ =** 167.0, 138.8, 128.7, 128.7, 126.7, 47.7, 44.0, 41.8, 34.7, 18.5. **IR (neat):** ν = 2960, 1740, 1399, 700 cm^{-1}. **HRMS (ESI):** Calculated for $C_{12}H_{15}NNaO$ ($[M+Na]^+$): 212.1246; found: 212.1246

4-methyl-1-(3-phenylpropyl)azetidin-2-one 4.12p



Chemical Formula: $C_{13}H_{17}NO$
Exact Mass: 203.1310

Conditions A: Double-chamber system:

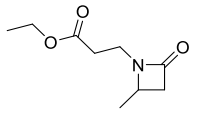
Following general procedure **A**, Chamber A was filled with $Pd(OAc)_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(*t*-Bu)$_3$●HBF_4 (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy_2NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with isopropyl(3-phenylpropyl)carbamoyl chloride **4.11p** (31.9 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing 4-methyl-1-(3-phenylpropyl)azetidin-2-one **4.12p** (21.9 mg, 0.108 mmol, 81 %).

Conditions B: CO atmosphere

Following general procedure **B**, isopropyl(3-phenylpropyl)carbamoyl chloride **4.11p** (31.9 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C, the excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing 4-methyl-1-(3-phenylpropyl)azetidin-2-one **4.12p** (16.0 mg, 0.078 mmol, 59 %).

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 7.26 – 7.17 (m, 2H), 7.15 – 7.07 (m, 3H), 3.60 – 3.52 (m, 1H), 3.31 – 3.22 (m, 1H), 3.02 – 2.91 (m, 2H), 2.57 (t, *J* = 7.7 Hz, 2H), 2.40 (dd, *J* = 14.4, 2.2 Hz, 1H), 1.84 – 1.74 (m, 2H), 1.23 (d, *J* = 6.1 Hz, 3H). **^{13}C NMR ($CDCl_3$, 101 MHz) :** δ = 167.1, 141.3, 128.6, 128.4, 126.1, 47.3, 43.9, 40.0, 33.5, 29.9, 18.8. **IR (neat):** ν = 2925, 1738, 1400, 701 cm^{-1}. **HRMS (ESI):** Calculated for $C_{13}H_{17}NNaO_4$ ($[M+Na]^+$): 226.1202; found: 226.1203

Methyl 3-(2-methyl-4-oxoazetidin-1-yl)propanoate 4.12q



Chemical Formula: $C_9H_{15}NO_3$
Exact Mass: 185.1052

Conditions A: Double-chamber system:

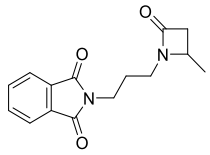
Following general procedure **A**, Chamber A was filled with $Pd(OAc)_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(*t*-Bu)$_3$●HBF_4 (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy_2NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with methyl 3-((chlorocarbonyl)(isopropyl)amino)propanoate **4.11q** (29.5 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing Methyl 3-(2-methyl-4-oxoazetidin-1-yl)propanoate **4.12q** (12.5 mg, 0.065 mmol, 50 %).

Conditions B: CO atmosphere

Following general procedure **B**, methyl 3-((chlorocarbonyl)(isopropyl)amino)propanoate **4.11q** (29.5 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C, the excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing Methyl 3-(2-methyl-4-oxoazetidin-1-yl)propanoate **4.12q** (12 mg, 0.060 mmol, 49 %).

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 4.15 (q, *J* = 7.1 Hz, 2H), 3.72 – 3.64 (m, 1H), 3.60 (dt, *J* = 14.5, 6.5 Hz, 1H), 3.33 – 3.23 (m, 1H), 3.03 (dd, *J* = 14.5, 4.9 Hz, 1H), 2.66 – 2.50 (m, 2H), 2.47 (dd, *J* = 14.5, 2.3 Hz, 1H), 1.32 (d, *J* = 6.1 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR ($CDCl_3$, 101 MHz) :** δ = 171.6, 167.1, 60.1, 48.0, 44.2, 36.0, 33.6, 18.7, 14.3. **IR (neat):** ν = 2923, 1737, 1396, 1183 cm^{-1}. **HRMS (ESI):** Calculated for $C_9H_{15}NNaO_3$ ($[M+Na]^+$): 208.0944; found: 208.0946

2-(3-(2-methyl-4-oxoazetidin-1-yl)propyl)isoindoline-1,3-*di*one 4.12r



Chemical Formula: $C_{15}H_{16}N_2O_3$
Exact Mass: 272.1161

Conditions A: Double-chamber system:

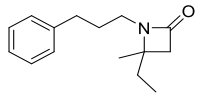
Following general procedure **A**, Chamber A was filled with $Pd(OAc)_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(*t*-Bu)$_3$●HBF_4 (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy_2NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with (3-(1,3-dioxoisoindolin-2-yl)propyl)(isopropyl)carbamoyl chloride **4.11r** (41.1 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing 2-(3-(2-methyl-4-oxoazetidin-1-yl)propyl)isoindoline-1,3-dione **4.12r** (15.6 mg, 0.057 mmol, 43 %).

Conditions B: CO atmosphere

Following general procedure **B**, (3-(1,3-dioxoisoindolin-2-yl)propyl)(isopropyl)carbamoyl chloride **4.11r** (41.1 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C, the excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing 2-(3-(2-methyl-4-oxoazetidin-1-yl)propyl)isoindoline-1,3-dione **4.12r** (8.0 mg, 0.029 mmol, 22 %).

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 7.87 – 7.80 (m, 2H), 7.76 – 7.69 (m, 2H), 3.82 – 3.66 (m, 3H), 3.46 – 3.31 (m, 1H), 3.15 – 3.01 (m, 2H), 2.50 (dd, *J* = 14.5, 2.3 Hz, 1H), 2.01 – 1.85 (m, 3H), 1.34 (d, *J* = 6.1 Hz, 3H). **^{13}C NMR ($CDCl_3$, 101 MHz) :** δ = 168.4, 167.2, 134.2, 132.2, 123.4, 47.6, 44.1, 38.1, 35.8, 27.3, 18.9. **IR (neat):** ν = 1711, 1742, 1397, 722 cm^{-1}. **HRMS (ESI):** Calculated for $C_{15}H_{16}N_2NaO_3$ ($[M+Na]^+$): 295.1059; found: 295.1057

4-ethyl-4-methyl-1-(3-phenylpropyl)azetidin-2-one 4.12s



Chemical Formula: $C_{15}H_{21}NO$
Exact Mass: 231.1623

Conditions A: Double-chamber system:

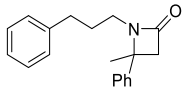
Following general procedure **A**, Chamber A was filled with $Pd(OAc)_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(*t*-Bu)$_3$●HBF_4 (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy_2NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with tert-pentyl(3-phenylpropyl)carbamoyl chloride **4.11s** (35.6 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing 4-ethyl-4-methyl-1-(3-phenylpropyl)azetidin-2-one **4.12s** (22.5 mg, 0.097 mmol, 73 %).

Conditions B: CO atmosphere

Following general procedure **B**, *tert*-pentyl(3-phenylpropyl)carbamic chloride **4.11s** (35.6 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C, the excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing 4-ethyl-4-methyl-1-(3-phenylpropyl)azetidin-2-one **4.12s** (22.2 mg, 0.096 mmol, 72 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 – 7.17 (m, 5H), 3.21 – 3.03 (m, 2H), 2.75 (d, *J* = 14.3 Hz, 1H), 2.70 – 2.61 (m, 2H), 2.57 (d, *J* = 14.4 Hz, 1H), 1.95 – 1.85 (m, 2H), 1.76 – 1.67 (m, 1H), 1.64 – 1.55 (m, 1H), 1.35 (s, 3H), 0.92 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR ($CDCl_3$, 101 MHz) :** δ = 167.1, 141.4, 128.5, 128.5, 126.1, 58.8, 47.1, 39.4, 33.7, 31.0, 30.8, 23.1, 9.1. **IR (neat):** ν = 2924, 1739, 1399, 733 cm^{-1}. **HRMS (ESI):** Calculated for $C_{15}H_{22}NO$ ($[M+H]^+$): 232.1696; found: 232.1699

4-methyl-4-phenyl-1-(3-phenylpropyl)azetidin-2-one 4.12t



Chemical Formula: $C_{19}H_{21}NO$
Exact Mass: 279.1623

Conditions A: Double-chamber system:

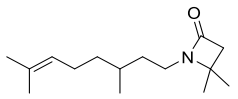
Following general procedure **A**, Chamber A was filled with $Pd(OAc)_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(*t*-Bu)$_3$●HBF_4 (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy_2NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with (2-phenylpropan-2-yl)(3-phenylpropyl)carbamoyl chloride **4.11t** (42 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing 4-methyl-4-phenyl-1-(3-phenylpropyl)azetidin-2-one **4.12t** (20.8 mg, 0.074 mmol, 56 %).

Conditions B: CO atmosphere

Following general procedure **B**, (2-phenylpropan-2-yl)(3-phenylpropyl)carbamoyl chloride **4.11t** (42 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C, the excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing 4-methyl-4-phenyl-1-(3-phenylpropyl)azetidin-2-one **4.12t** (21.2 mg, 0.076 mmol, 57 %).

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 7.42 – 7.07 (m, 10H), 3.32 – 3.24 (m, 1H), 3.03 (s, 2H), 3.01 – 2.95 (m, 1H), 2.69 – 2.53 (m, 2H), 1.92 – 1.80 (m, 2H), 1.84 (s, 3H). **^{13}C NMR ($CDCl_3$, 101 MHz) :** δ = 167.7, 142.1, 141.3, 128.9, 128.5, 128.4, 127.9, 126.1, 125.6, 59.0, 53.9, 40.5, 33.7, 30.4, 23.4. **IR (neat):** ν = 2926, 1743, 1395, 732 cm^{-1}. **HRMS (ESI):** Calculated for $C_{19}H_{21}NNaO$ ($[M+Na]^+$): 302.1515; found: 302.1517

1-(3,7-*d*imethyloct-6-en-1-yl)-4,4-*d*imethylazetidin-2-one 4.12u



Chemical Formula: $C_{15}H_{27}NO$
Exact Mass: 237.2093

Conditions A: Double-chamber system:

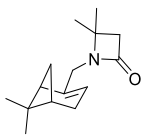
Following general procedure **A**, Chamber A was filled with $Pd(OAc)_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(*t*-Bu)$_3$●HBF_4 (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy_2NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with tert-butyl(3,7-dimethyloct-6-en-1-yl)carbamoyl chloride **4.11u** (36.4 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing 1-(3,7-dimethyloct-6-en-1-yl)-4,4-dimethylazetidin-2-one **4.12u** (31.6 mg, 0.133 mmol, 100 %).

Conditions B: CO atmosphere

Following general procedure **B**, *tert*-butyl(3,7-dimethyloct-6-en-1-yl)carbamoyl chloride **4.11u** (36.4 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C, the excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing 1-(3,7-dimethyloct-6-en-1-yl)-4,4-dimethylazetidin-2-one **4.12u** (24 mg, 0.101 mmol, 76 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.12 – 5.02 (m, 1H), 3.09 (t, *J* = 7.7 Hz, 2H), 2.68 (s, 2H), 2.03 – 1.88 (m, 2H), 1.69 – 1.65 (m, 3H), 1.58 (s, 3H), 1.36 (s, 6H), 1.54 – 1.09 (m, 5H), 0.90 (d, *J* = 6.3 Hz, 3H). **^{13}C NMR ($CDCl_3$, 101 MHz):** δ = 166.5, 131.5, 124.7, 55.4, 50.4, 37.7, 37.0, 36.1, 30.6, 25.8, 25.5, 25.3, 19.3, 17.8. **IR (neat):** ν = 2925, 1736, 1402, 911, 732cm^{-1}. **HRMS (ESI):** Calculated for $C_{15}H_{27}NNaO$ ($[M+Na]^+$): 260.1985; found: 260.1985

1-(((1*R*,5*S*)-6,6-*di*methylbicyclo[3.1.1]hept-2-en-2-yl)methyl)-4,4-*di*methylazetidin-2-one 4.12v



Chemical Formula: $C_{15}H_{23}NO$
Exact Mass: 233.1780

Conditions A: Double-chamber system:

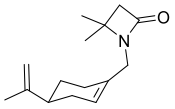
Following general procedure **A**, Chamber A was filled with $Pd(OAc)_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(*t*-Bu)$_3$●HBF_4 (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy_2NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with tert-butyl(((1*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl)carbamoyl chloride **4.11v** (35.9 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing 1-(((1*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl)-4,4-dimethylazetidin-2-one **4.12v** (16.5 mg, 0.07 mmol, 53 %).

Conditions B: CO atmosphere

Following general procedure **B**, *tert*-butyl(((1*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl)carbamoyl chloride **4.11v** (35.9 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C, the excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing 1-(((1*R*,5*S*)-6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)methyl)-4,4-dimethylazetidin-2-one **4.12v** (15.5 mg, 0.067 mmol, 50 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.46 – 5.40 (m, 1H), 3.82 (dq, *J* = 15.5, 2.2 Hz, 1H), 3.38 (d, *J* = 15.5 Hz, 1H), 2.71 (s, 2H), 2.39 (dt, *J* = 8.6, 5.6 Hz, 1H), 2.29 – 2.18 (m, 2H), 2.17 – 2.14 (m, 1H), 2.11 – 2.01 (m, 1H), 1.35 (d, *J* = 5.9 Hz, 6H), 1.27 (s, 3H), 1.13 (d, *J* = 8.6 Hz, 1H), 0.81 (s, 3H). **^{13}C NMR ($CDCl_3$, 101 MHz):** δ = 166.9, 144.1, 120.1, 55.7, 50.6, 44.3, 43.8, 40.7, 38.2, 31.8, 31.4, 26.2, 26.0, 24.6, 21.0. **IR (neat):** ν = 1731, 907, 728 cm^{-1}. **HRMS (ESI):** Calculated for $C_{15}H_{23}NNaO$ ($[M+Na]^+$): 256.1672; found: 256.1672 **Optical rotation :** $[\alpha]_D^{20}$ = -59.1° (c = 0.8, $CHCl_3$)

(*S*)-4,4-*d*imethyl-1-((4-(prop-1-en-2-yl)cyclohex-1-en-1-yl)methyl)azetidin-2-one 4.12w



Chemical Formula: $C_{15}H_{23}NO$
Exact Mass: 233.1780

Conditions A: Double-chamber system:

Following general procedure **A**, Chamber A was filled with $Pd(OAc)_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(*t*-Bu)$_3$●HBF_4 (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy_2NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with (*S*)-tert-butyl((4-(prop-1-en-2-yl)cyclohex-1-en-1-yl)methyl)carbamoyl chloride **4.11w** (35.9 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography

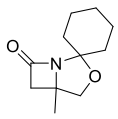
using cyclohexane/AcOEt as eluent, providing (*S*)-4,4-dimethyl-1-((4-(prop-1-en-2-yl)cyclohex-1-en-1-yl)methyl)azetidin-2-one **4.12w** (18.9 mg, 0.081 mmol, 68 %).

Conditions B: CO atmosphere

Following general procedure **B**, (*S*)-*tert*-butyl((4-(prop-1-en-2-yl)cyclohex-1-en-1-yl)methyl)carbamoyl **4.11w** (35.9 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C, the excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing (*S*)-4,4-dimethyl-1-((4-(prop-1-en-2-yl)cyclohex-1-en-1-yl)methyl)azetidin-2-one **4.12w** (18.3 mg, 0.078 mmol, 59 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.66 – 5.60 (m, 1H), 4.74 – 4.67 (m, 2H), 3.70 (d, *J* = 15.0 Hz, 1H), 3.57 (d, *J* = 15.0 Hz, 1H), 2.72 (s, 2H), 2.21 – 1.77 (m, 7H), 1.75 – 1.71 (m, 3H), 1.35 (d, *J* = 6.4 Hz, 6H). **^{13}C NMR ($CDCl_3$, 101 MHz):** δ = 166.9, 149.7, 133.5, 124.9, 108.8, 55.9, 50.8, 45.6, 41.0, 30.8, 27.6, 26.9, 25.2, 24.8, 20.9. **IR (neat):** ν = 2921, 1745, 1392, 732 cm^{-1}. **HRMS (ESI):** Calculated for $C_{15}H_{23}NNaO$ ($[M+Na]^+$): 256.1672 found: 256.1672. **Optical rotation :** $[\alpha]_D^{20}$ = -65.5° (c = 1.1, $CHCl_3$)

5-methyl-3-oxa-1-azaspiro[bicyclo[3.2.0]heptane-2,1'-cyclohexan]-7-one 4.12x



Chemical Formula: $C_{11}H_{17}NO_2$
Exact Mass: 195.1259

Conditions A: Double-chamber system:

Following general procedure **A**, Chamber A was filled with $Pd(OAc)_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(*t*-Bu)$_3$●HBF_4 (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy_2NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with 3,3-dimethyl-1-oxa-4-azaspiro[4.5]decane-4-carbamoyl chloride **4.11x** (30.8 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The excess of mesitylene was removed by flushing cyclohexane

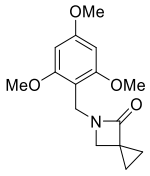
on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing 2x (18.2 mg, 0.093 mmol, 70 %).

Conditions B: CO atmosphere

Following general procedure **B**, ethyl(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11x** (30.8 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C, the excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing 5-methyl-3-oxa-1-azaspiro[bicyclo[3.2.0]heptane-2,1'-cyclohexan]-7-one **4.12x** (18.2 mg, 0.093 mmol, 70 %).

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 3.89 (d, *J* = 9.0 Hz, 1H), 3.82 (d, *J* = 9.0 Hz, 1H), 2.91 (d, *J* = 15.9 Hz, 1H), 2.86 (d, *J* = 16.0 Hz, 1H), 2.21 (m, 1H), 1.88 – 1.56 (m, 6H), 1.55 (s, 3H), 1.53 – 1.39 (m, 3H). **^{13}C NMR ($CDCl_3$, 101 MHz):** δ = 175.4, 98.5, 73.9, 59.1, 47.7, 35.9, 32.7, 25.2, 24.5, 23.9, 23.5. **IR (neat):** ν = 2935, 2859, 1768, 1450, 1264, 913, 731 cm^{-1}. **HRMS (ESI):** Calculated for $C_{11}H_{17}NNaO_2$ ($[M+Na]^+$): 218.1151; found: 218.1150

5-(2,4,6-trimethoxybenzyl)-5-azaspiro[2.3]hexan-4-one 4.12y



Chemical Formula: $C_{15}H_{19}NO_4$
Exact Mass: 277.1314

Conditions A: Double-chamber system:

Following general procedure **A**, Chamber A was filled with $Pd(OAc)_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(*t*-Bu)$_3$●HBF_4 (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy_2NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with (cyclopropylmethyl)(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11y** (41.7 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The excess of mesitylene was removed by flushing cyclohexane

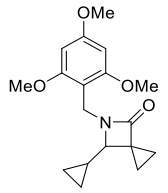
on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing 2y (27.6 mg, 0.100 mmol, 75 %).

Conditions B: CO atmosphere

Following general procedure **B**, ((cyclopropylmethyl)(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11y** (41.7 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C, the excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing 5-(2,4,6-trimethoxybenzyl)-5-azaspiro[2.3]hexan-4-one **4.12y** (27.7 mg, 0.102 mmol, 76 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.13 (s, 2H), 4.47 (s, 2H), 3.84 – 3.79 (m, 9H), 3.21 (s, 2H), 1.14 – 1.06 (m, 2H), 0.86 – 0.79 (m, 2H). **^{13}C NMR ($CDCl_3$, 101 MHz):** δ = 172.0, 161.2, 159.7, 104.7, 90.5, 55.9, 55.5, 48.5, 34.4, 31.6, 7.3. **IR (neat):** ν = 2968, 1745, 1608, 1147, 669 cm^{-1}. **HRMS (ESI):** Calculated for $C_{15}H_{19}NNaO_4$ ($[M+Na]^+$): 300.1206; found: 300.1208

6-cyclopropyl-5-(2,4,6-trimethoxybenzyl)-5-azaspiro[2.3]hexan-4-one 4.12z



Chemical Formula: $C_{18}H_{23}NO_4$
Exact Mass: 317.1627

Conditions A: Double-chamber system:

Following general procedure **A**, Chamber A was filled with $Pd(OAc)_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(*t*-Bu)$_3$●HBF_4 (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy_2NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with (dicyclopropylmethyl)(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11z** (47.1 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt

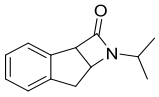
as eluent, providing 6-cyclopropyl-5-(2,4,6-trimethoxybenzyl)-5-azaspiro[2.3]hexan-4-one **4.12z** (34 mg, 0.107 mmol, 81 %).

Conditions B: CO atmosphere

Following general procedure **B**, (dicyclopropylmethyl)(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11z** (47.1 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C, the excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing 6-cyclopropyl-5-(2,4,6-trimethoxybenzyl)-5-azaspiro[2.3]hexan-4-one **4.12z** (34 mg, 0.107 mmol, 81 %).

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 6.10 (s, 2H), 4.59 (d, *J* = 14.0 Hz, 1H), 4.41 (d, *J* = 14.0 Hz, 1H), 3.82 – 3.78 (m, 9H), 2.55 (d, *J* = 9.3 Hz, 1H), 1.16 – 0.98 (m, 1H), 0.95 – 0.85 (m, 1H), 0.83 – 0.73 (m, 1H), 0.71 – 0.58 (m, 1H), 0.41 – 0.26 (m, 2H), -0.02 – -0.11 (m, 1H), -0.19 – -0.28 (m, 1H). **^{13}C NMR ($CDCl_3$, 101 MHz):** δ = 172.4, 161.0, 159.7, 104.9, 90.3, 64.1, 55.7, 36.6, 33.5, 11.6, 7.2, 5.9, 2.4, 0.1. **IR (neat):** ν = 2937, 1736, 1597, 1138, 728 cm^{-1}. **HRMS (ESI):** Calculated for $C_{18}H_{23}NNaO_4$ ($[M+Na]^+$): 340.1519; found: 340.1523

1-isopropyl-1,2a,7,7a-tetrahydro-2H-indeno[2,1-b]azet-2-one 4.12aa



Chemical Formula: $C_{13}H_{15}NO$
Exact Mass: 201.1154

Conditions A: Double-chamber system:

Following general procedure **A**, Chamber A was filled with $Pd(OAc)_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(*t*-Bu)$_3$●HBF_4 (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy_2NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with (2,3-dihydro-1H-inden-2-yl)(isopropyl)carbamoyl chloride **4.11aa** (31.6 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt

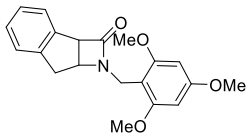
as eluent, providing 1-isopropyl-1,2a,7,7a-tetrahydro-2H-indeno[2,1-b]azet-2-one **4.12aa** (20.9 mg, 0.104 mmol, 78 %).

Conditions B: CO atmosphere

Following general procedure **B**, (2,3-dihydro-1H-inden-2-yl)(isopropyl)carbamoyl chloride **4.11aa** (31.6 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C, the excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing 1-isopropyl-1,2a,7,7a-tetrahydro-2H-indeno[2,1-b]azet-2-one **4.12aa** (20.9 mg, 0.104 mmol, 78 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 – 7.39 (m, 1H), 7.25 – 7.19 (m, 3H), 4.48 (d, *J* = 4.0 Hz, 1H), 4.40 (ddd, *J* = 6.3, 4.0, 1.3 Hz, 1H), 3.83 (hept, *J* = 6.8 Hz, 1H), 3.24 – 2.99 (m, 3H), 1.30 (d, *J* = 6.8 Hz, 3H), 1.23 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR ($CDCl_3$, 101 MHz):** δ = 168.5, 142.1, 137.7, 127.9, 127.4, 126.3, 125.2, 61.5, 53.6, 44.3, 35.4, 22.1, 20.7. **IR (neat):** ν = 2973, 1742, 672 cm^{-1}. **HRMS (ESI):** Calculated for $C_{13}H_{15}NNaO$ ($[M+Na]^+$): 224.1046; found: 224.1043

1-(2,4,6-trimethoxybenzyl)-1,2a,7,7a-tetrahydro-2H-indeno[2,1-b]azet-2-one 4.12ab



Chemical Formula: $C_{20}H_{21}NO_4$
Exact Mass: 339.1471

Conditions A: Double-chamber system:

Following general procedure **A**, Chamber A was filled with $Pd(OAc)_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(*t*-Bu)$_3$●HBF_4 (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy_2NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with (2,3-dihydro-1H-inden-2-yl)(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11ab** (52 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography

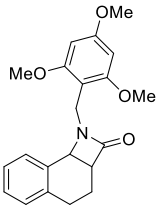
using cyclohexane/AcOEt as eluent, providing 1-(2,4,6-trimethoxybenzyl)-1,2a,7,7a-tetrahydro-2H-indeno[2,1-b]azet-2-one **4.12ab** (42 mg, 0.124mmol, 93 %).

Conditions B: CO atmosphere

Following general procedure **B**, (2,3-dihydro-1H-inden-2-yl)(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11ab** (52 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C, the excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing 1-(2,4,6-trimethoxybenzyl)-1,2a,7,7a-tetrahydro-2H-indeno[2,1-b]azet-2-one **4.12ab** (30.6 mg, 0.09 mmol, 68 %).

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 7.44 – 7.39 (m, 1H), 7.23 – 7.16 (m, 3H), 6.13 (s, 2H), 4.56 (d, *J* = 13.9 Hz, 1H), 4.43 (d, *J* = 3.9 Hz, 1H), 4.20 (d, *J* = 13.9 Hz, 1H), 4.12 – 4.05 (m, 1H), 3.83 (s, 3H), 3.80 (s, 6H), 3.06 (d, *J* = 17.6 Hz, 1H), 2.82 (dd, *J* = 17.5, 6.8 Hz, 1H). **^{13}C NMR ($CDCl_3$, 101 MHz) :** δ = 168.3, 161.3, 159.6, 142.7, 138.1, 127.7, 127.1, 126.2, 125.2, 104.4, 90.4, 62.0, 55.8, 55.5, 55.1, 33.3, 32.2. **IR (neat):** ν = 2939, 1737, 1596, 1459, 1131, 728 cm^{-1}. **HRMS (ESI):** Calculated for $C_{20}H_{21}NNaO_4$ ($[M+Na]^+$): 362.1363; found: 362.1365

1-(2,4,6-trimethoxybenzyl)-2a,3,4,8b-tetrahydronaphtho[1,2-b]azet-2(1H)-one 4.12ac



Chemical Formula: $C_{21}H_{23}NO_4$
Exact Mass: 353.1627

Conditions A: Double-chamber system:

Following general procedure **A**, Chamber A was filled with $Pd(OAc)_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(*t*-Bu)$_3$●HBF_4 (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy_2NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with (1,2,3,4-tetrahydronaphthalen-1-yl)(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11ac** (51.9 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30

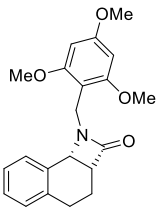
mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing 1-(2,4,6-trimethoxybenzyl)-2a,3,4,8b-tetrahydronaphtho[1,2-b]azet-2(1H)-one **4.12ac** (47.0 mg, 0.133 mmol, 100 %).

Conditions B: CO atmosphere

Following general procedure **B**, (1,2,3,4-tetrahydronaphthalen-1-yl)(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11ac** (51.9 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C, the excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing 1-(2,4,6-trimethoxybenzyl)-2a,3,4,8b-tetrahydronaphtho[1,2-b]azet-2(1H)-one **4.12ac** (22.6 mg, 0.064 mmol, 48 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 – 7.12 (m, 1H), 7.12 – 7.06 (m, 1H), 7.02 (s, 1H), 6.80 (dd, *J* = 7.4, 1.3 Hz, 1H), 6.00 (s, 2H), 4.44 (d, *J* = 13.9 Hz, 1H), 4.31 (d, *J* = 4.9 Hz, 1H), 4.04 (d, *J* = 13.8 Hz, 1H), 3.80 (s, 3H), 3.73 (s, 6H), 3.55 – 3.47 (m, 1H), 2.86 – 2.56 (m, 2H), 2.37 – 2.24 (m, 1H), 1.57 – 1.36 (m, 1H). **^{13}C NMR ($CDCl_3$, 101 MHz):** δ = 169.4, 161.2, 159.6, 139.9, 133.2, 130.6, 128.4, 127.8, 125.6, 103.8, 90.2, 55.6, 55.5, 53.6, 49.7, 33.0, 27.0, 23.0. **IR (neat):** ν = 2935, 1737, 1597, 1133 cm^{-1}. **HRMS (ESI):** Calculated for $C_{21}H_{23}NNaO_4$ ($[M+Na]^+$): 376.1519; found: 376.1521

2(a*R*,8b*R*)-1-(2,4,6-trimethoxybenzyl)-2a,3,4,8b-tetrahydronaphtho[1,2-b]azet-2(1H)-one (-)-4.12ac



Chemical Formula: $C_{21}H_{23}NO_4$
Exact Mass: 353.1627

Standard synthesis:

Conditions A: Double-chamber system:

Following general procedure **A**, Chamber A was filled with $Pd(OAc)_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(*t*-Bu)$_3$●HBF_4 (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy_2NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with (1,2,3,4-tetrahydronaphthalen-1-yl)(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11ac** (51.9 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing 2(a*R*,8b*R*)-1-(2,4,6-trimethoxybenzyl)-2a,3,4,8b-tetrahydronaphtho[1,2-b]azet-2(1H)- one **(-)-4.12ac** (46.0 mg, 0.130 mmol, 98 %).

Conditions B: CO atmosphere

Following general procedure **B**, (1,2,3,4-tetrahydronaphthalen-1-yl)(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11ac** (51.9 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C, the excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing 2(a*R*,8b*R*)-1-(2,4,6-trimethoxybenzyl)-2a,3,4,8b-tetrahydronaphtho[1,2-b]azet-2(1H)- one **(-)-4.12ac** (32 mg, 0.09 mmol, 63 %).

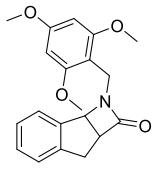
Tenfold scale synthesis:

Conditions A: Double-chamber system:

Following general procedure **A**, Chamber A was filled with $Pd(OAc)_2$ (89 mg, 0.4 mmol, 30 mol%), P(*t*-Bu)$_3$●HBF_4 (120 mg, 0.4 mmol, 30 mol%), COgen (970 mg, 4 mmol, 3.0 equiv), Cy_2NMe (1.610 g, 7.98 mmol, 6.0 equiv) and mesitylene (5 mL). Chamber B, previously charged with (1,2,3,4-tetrahydronaphthalen-1-yl)(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11ac** (519 mg, 1.33 mmol, 1 equiv) was reacted with $PdCl_2$ (24 mg, 0.133 mmol, 10 mol%), cataCXium AHI (120 mg , 0.266 mmol, 20 mol%), pivalic acid (41 mg, 0.4 mmol, 30 mol%) and cesium carbonate (1.30 g, 4 mmol, 3.0 equiv) in mesitylene (26.2 mL). The two chambers system was reacted for 18h at 120 °C. The excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing 2(a*R*,8b*R*)-1-(2,4,6-trimethoxybenzyl)-2a,3,4,8b-tetrahydronaphtho[1,2-b]azet-2(1H)- one **(-)-4.12ac** (385 mg, 1.09 mmol, 82 %).

^{1}H NMR (250 MHz, $CDCl_3$) δ = 7.19 – 7.12 (m, 1H), 7.11 – 6.98 (m, 2H), 6.80 (dd, *J* = 7.4, 1.3 Hz, 1H), 5.99 (s, 2H), 4.44 (d, *J* = 13.9 Hz, 1H), 4.31 (d, *J* = 4.9 Hz, 1H), 4.04 (d, *J* = 13.8 Hz, 1H), 3.80 (s, 3H), 3.73 (s, 6H), 3.51 (t, *J* = 5.3 Hz, 1H), 2.85 – 2.58 (m, 2H), 2.37 – 2.22 (m, 1H), 1.58 – 1.42 (m, 1H). **^{13}C NMR (63 MHz, $CDCl_3$) δ =** 169.4, 161.2, 159.6, 139.9, 133.2, 130.6, 128.4, 127.8, 125.6, 103.8, 90.2, 55.6, 55.5, 53.6, 49.7, 33.0, 27.0, 23.0. **IR (neat):** ν = 2935, 1737, 1597, 1133 cm^{-1}. **HRMS (ESI):** Calculated for $C_{21}H_{23}NNaO_4$ ($[M+Na]^+$): 376.1519; found: 376.1524 **Optical rotation :** $[\alpha]_D^{20}$ = -38.8° (c = 1.3, $CHCl_3$)

1-(2,4,6-trimethoxybenzyl)-1,2a,3,7b-tetrahydro-2H-indeno[1,2-b]azet-2-one 4.12ad



Chemical Formula: $C_{20}H_{21}NO_4$
Exact Mass: 339.1471
2ad

Conditions A: Double-chamber system:

Following general procedure **A**, Chamber A was filled with $Pd(OAc)_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(*t*-Bu)$_3$●HBF_4 (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy_2NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with (2,3-dihydro-1H-inden-1-yl)(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11ad** (50 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%),

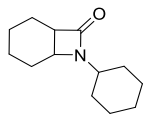
cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing 1-(2,4,6-trimethoxybenzyl)-1,2a,3,7b-tetrahydro-2H-indeno[1,2-b]azet-2-one **4.12ad** (21 mg, 0.062 mmol, 47 %).

Conditions B: CO atmosphere

Following general procedure **B**, (2,3-dihydro-1H-inden-1-yl)(2,4,6-trimethoxybenzyl)carbamoyl chloride **4.11ad** (50 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C, the excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing 1-(2,4,6-trimethoxybenzyl)-1,2a,3,7b-tetrahydro-2H-indeno[1,2-b]azet-2-one **4.12ad** (11 mg, 0.032 mmol, 25 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.28 – 7.23 (m, 2H), 7.15 – 7.11 (m, 2H), 6.13 (s, 2H), 4.72 (dd, *J* = 4.2, 1.0 Hz, 1H), 4.56 (d, *J* = 14.1 Hz, 1H), 4.04 (d, *J* = 14.1 Hz, 1H), 3.85 – 3.82 (m, 10H), 3.36 – 3.27 (m, 1H), 2.97 (dd, *J* = 17.4, 10.4 Hz, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 169.7, 161.3, 159.7, 145.2, 139.6, 128.7, 126.4, 126.4, 126.0, 104.7, 90.5, 62.0, 55.8, 55.5, 52.3, 33.0, 30.2. **IR (neat):** ν = 1743, 670 cm^{-1}. **HRMS (ESI):** Calculated for $C_{20}H_{21}NNaO_4$ ($[M+Na]^+$): 312.1368; found: 312.1369

7-cyclohexyl-7-azabicyclo[4.2.0]octan-8-one 4.12ae



Chemical Formula: $C_{13}H_{21}NO$
Exact Mass: 207.1623

Conditions A: Double-chamber system:

Following general procedure **A**, Chamber A was filled with $Pd(OAc)_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(*t*-Bu)$_3$●HBF_4 (12 mg, 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy_2NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with dicyclohexylcarbamoyl chloride **4.11ae** (32.4 mg, 0.133 mmol, 1 equiv) was

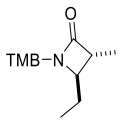
reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing 7-cyclohexyl-7-azabicyclo[4.2.0]octan-8-one **4.12ae** (8.5 mg, 0.041 mmol, 29 %).

Conditions B: CO atmosphere

Following general procedure **B**, dicyclohexylcarbamoyl chloride **4.11ae** (32.4 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C, the excess of mesitylene was removed by flushing cyclohexane on silica gel, and the resulting crude was purified by chromatography using cyclohexane/AcOEt as eluent, providing 7-cyclohexyl-7-azabicyclo[4.2.0]octan-8-one **4.12ae** (7 mg, 0.034 mmol, 25 %).

^{1}H NMR (250 MHz, $CDCl_3$) δ = 3.78 (dt, *J* = 5.5, 3.6 Hz, 1H), 3.46 (ddt, *J* = 11.5, 7.8, 3.8 Hz, 1H), 3.08 (td, *J* = 5.6, 4.1 Hz, 1H), 1.89 – 1.20 (m, 22H + H_2O). **^{13}C NMR (63 MHz, $CDCl_3$)** δ = 170.3, 51.5, 49.3, 46.1, 32.0, 30.7, 25.4, 25.3, 24.7, 19.6, 18.7, 16.9. **IR (neat):** ν = 2932, 1732 cm^{-1}. **HRMS (ESI):** Calculated for $C_{13}H_{21}NNaO$ ($[M+Na]^+$): 230.1515; found: 230.1513

***Trans*-4-ethyl-3-methyl-1-(2,4,6-trimethoxybenzyl)azetidin-2-one and *Cis*-4-ethyl-3-methyl-1-(2,4,6-trimethoxybenzyl)azetidin-2-one 4.12af**



4.12af
d.r. 85:15

Conditions A : Two-chamber system:

Following general procedure **A**, Chamber A was filled with $Pd(OAc)_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(*t*-Bu)$_3$●HBF_4 (12 mg , 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy_2NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with Pentan-3-S78yl(2,4,6-trimethoxybenzyl)carbamoyl **4.11af** (43.9mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXium AHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate

(130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide *Trans*-4-ethyl-3-methyl-1-(2,4,6-trimethoxybenzyl)azetidin-2-one **4.12af** as major diastereoisomer (20 mg, 0.068 mmol, 51 %, d.r. 85:15).

Conditions B : CO atmosphere

Following general procedure **B**, Pentan-3-yl(2,4,6-trimethoxybenzyl)carbamoyl **4.11af** (43.9 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), cataCXiumAHI (12 mg, 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (130 mg, 0.4 mmol, 3.0 equiv) in mesitylene (2.62 mL), under CO atmosphere. The mixture was sztirred for 18h at 120°C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide *Trans*-4-ethyl-3-methyl-1-(2,4,6-trimethoxybenzyl)azetidin-2-one **4.12af** as major diastereoisomer (16 mg, 0.055 mmol, 41 %, d.r. 85:15).

Trans-4-ethyl-3-methyl-1-(2,4,6-trimethoxybenzyl)azetidin-2-one (major diastereoisomer)

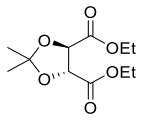
^{1}H NMR (250 MHz, $CDCl_3$) δ = 6.11 (s, 2H), 4.55 (d, *J* = 13.9 Hz, 1H), 4.16 (dd, *J* = 13.9, 1.1 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 6H), 2.78 –2.74 (m, 1H), 2.66 –2.61(m, 1H), 1.71 –1.63 (m, 1H), 1.34 –1.26 (m, 1H), 1.17 (d, *J* = 7.3 Hz, 3H), 0.81 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR (63 MHz, $CDCl_3$)** δ = 170.5, 161.1, 159.7, 104.5, 90.3, 60.9, 55.8, 55.4, 48.9, 32.7, 25.2, 13.4, 9.4. **IR (neat):** ν =2952, 1749, 1610, 1140, 740 cm^{-1}. **HRMS (ESI):** Calculated for $C_{16}H_{23}NNaO_4$ ($[M+Na]^+$): 316.1525; found: 316.1528

Cis-4-ethyl-3-methyl-1-(2,4,6-trimethoxybenzyl)azetidin-2-one (minor diastereoisomer) :

^{1}H NMR (250 MHz, $CDCl_3$) δ = 6.11 (s, 2H), 4.58 (d, *J* = 13.4 Hz, 1H), 4.11 (d, *J* = 14.0 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 6H), 3.18 –3.14 (m, 1H), 3.10 –3.04 (m, 1H), 1.72 –1.66 (m, 1H), 1.43 –1.35 (m, 1H), 1.16 (d, *J* = 6.6 Hz, 3H), 0.81 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR (63 MHz, $CDCl_3$)** δ = 171.0, 56.3, 55.8, 46.3, 32.6, 21.

3.10. Synthesis of phosphonites

Diethyl (4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate 4.15

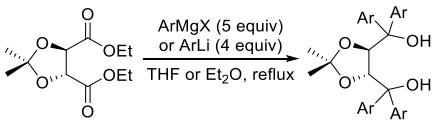


Chemical Formula: $C_{11}H_{18}O_6$
Exact Mass: 246.11034

To a stirred solution of (+)-diethyl L-tartrate (2,49 mL, 14.5 mmol) in toluene (30 mL) was added 2,2-dimethoxypropane (5,33 mL, 43.4 mmol, 3 equiv) and TsOH (125 mg, 0.725 mmol) at romm temperature. The mixture was refluxed overnight. The mixture was allowed to room temperature and was quenched with a $NaHCO_3$ solution. The biphasic mixture was extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude mixture was purified by silica gel chromatography to afford dimethyl 2,3-*O*-isopropylidene L-tartrate (3.35 g,13.62 mmol, 94%) as a colorless liquid.

^{1}H NMR (400 MHz, Chloroform-*d*) : δ = 4.65 (s, 2H), 4.17 (q, J = 7.2 Hz, 4H), 1.38 (s, 6H), 1.21 (t, J = 7.2 Hz, 7H). **Optical rotation :** $[\alpha]_D^{25}$ = – 39.3 (c = 1.0, $CHCl_3$) Lit.[189] $[\alpha]_D^{20}$ = -40.2° (c = 1.03, $CHCl_3$).

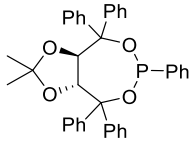
TADDOL **4.16a**[190], **4.16b**[191], **4.16c**[190], **4.16d**[190], **4.16e**[192], **4.16f**[193], **4.16g**[191] were prepared according to the general procedure "TADDOL" and the reaction scheme shown below. All spectral data were in accordance with the literature.



4.15
94%

4.16a : Ar = Ph : 44%
4.16b : Ar = 3,5-*t*-Bu: quant.
4.16c : Ar = 4-F : 83%
4.16d : Ar = 4-Tol : 88%
4.16e : Ar = C_6F_5 : 36%
4.16f : Ar = 3,5-*i*-Pr : 91%
4.16g : Ar = 3,5-CF_3 : 74%

(3a*R*,8a*R*)-2,2-Dimethyl-4,4,6,8,8-pentaphenyltetrahydro-[1,3]dioxolo[4,5e][1,3,2]dioxaphosphepine 4.16a

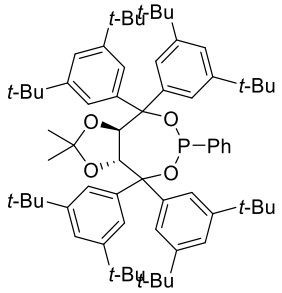


Chemical Formula: $C_{37}H_{33}O_4P$
Exact Mass: 572.21165

Following general procedure "Phosphonite", **4.16a** was obtained as a white solid (113 mg, 0.2 mmol, 66 %).

^{1}H NMR (400 MHz, Chloroform-*d*) : δ = 7.90 – 7.79 (m, 4H), 7.63 – 7.56 (m, 2H), 7.50 – 7.43 (m, 7H), 7.39 – 7.15 (m, 12H), 5.63 (dd, *J* = 8.6, 4.7 Hz, 1H), 4.79 (d, *J* = 8.6 Hz, 1H), 1.54 (s, 3H), 0.21 (s, 3H). **^{13}C NMR (101 MHz, Chloroform-*d*) :** δ = 146.9, 146.0 (d, $J_{C,P}$ = 3.8 Hz), 142.0 (d, $J_{C,P}$ = 1.7 Hz), 141.5 (d, $J_{C,P}$ = 2.2 Hz), 141.3 (d, $J_{C,P}$ = 10.9 Hz), 130.9, 130.2, 129.9, 129.5, 128.7, 128.7, 128.6, 128.5, 128.3, 128.1, 127.8, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 111.5, 84.1 (d, $J_{C,P}$ = 4.2 Hz), 83.4 (d, $J_{C,P}$ = 7.6 Hz), 82.7 (d, $J_{C,P}$ = 23.5 Hz), 82.3 (d, $J_{C,P}$ = 4.3 Hz), 28.0, 24.9. **^{31}P NMR (162 MHz, Chloroform-*d*) :** δ = 156.5. **Optical rotation :** $[\alpha]_D^{20}$ = +78.2° (c = 1.0, $CHCl_3$)

(3a*R*,8a*R*)-4,4,8,8-Tetrakis(3,5-*d*i-tert-butylphenyl)-2,2-*d*imethyl-6-phenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 4.16b



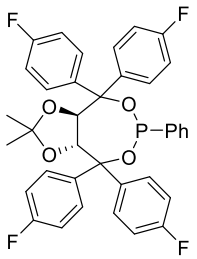
Chemical Formula: $C_{69}H_{97}O_4P$
Exact Mass: 1020.71245

Following general procedure "Phosphonite", **4.16b** was obtained as a white solid (211 mg, 0.207 mmol, 69 %).

^{1}H NMR (400 MHz, Chloroform-*d*) : δ = 7.92 – 7.85 (m, 2H), 7.58 – 7.53 (m, 2H), 7.46 – 7.43 (m, 2H), 7.39 – 7.36 (m, 3H), 7.34 – 7.30 (m, 2H), 7.18 – 7.13 (m, 2H), 7.12 – 7.08 (m, 2H), 7.05 – 7.03 (m, 2H), 5.49 (dd, *J* = 8.7, 3.6 Hz, 1H), 4.79 (d, *J* = 8.7 Hz, 1H), 1.46 (s, 3H), 1.18 (s, 18H), 1.15 (s, 18H), 1.14 (s, 18H), 1.12 (s, 18H), 0.00 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) : δ = 149.8 (d, $J_{C,P}$ = 23.0 Hz), 149.0 (d, $J_{C,P}$ = 9.8 Hz), 146.5, 145.7 (d, $J_{C,P}$ = 4.2 Hz), 142.7 (d, $J_{C,P}$ = 11.6 Hz), 141.7 (d, $J_{C,P}$ = 1.8 Hz), 140.7 (d, $J_{C,P}$ = 1.3 Hz), 130.7, 130.3, 130.1, 128.3, 128.3, 124.0, 122.4, 121.8, 120.9, 120.6, 120.6, 120.4, 110.2, 84.5 (d, $J_{C,P}$ = 4.6 Hz), 84.4 (d, $J_{C,P}$ = 7.3 Hz), 84.2 (d, $J_{C,P}$ = 19.7 Hz), 83.3 (d, $J_{C,P}$ = 5.3 Hz), 35.2, 35.1, 34.9, 31.7, 31.7, 31.6, 31.6, 31.5, 28.3, 23.8. **^{31}P NMR (162 MHz, Chloroform-*d*) :** δ = 155.0. **Optical rotation :** $[\alpha]_D^{20}$ = -40.2° (c = 1.0, $CHCl_3$)

(3a*R*,8a*R*)-4,4,8,8-Tetrakis(4-fluorophenyl)-2,2-dimethyl-6-phenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 4.16c

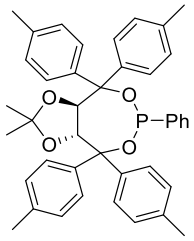


Chemical Formula: $C_{37}H_{29}F_4O_4P$
Exact Mass: 644.17396

Following general procedure "Phosphonite", **4.16c** was obtained as a white solid (174 mg, 0.27 mmol, 90 %).

^{1}H NMR (400 MHz, Chloroform-*d*) : δ = 7.91 – 7.76 (m, 4H), 7.63 – 7.52 (m, 4H), 7.51 – 7.36 (m, 4H), 7.19 – 6.94 (m, 9H), 5.53 (dd, *J* = 8.7, 4.7 Hz, 1H), 4.70 (d, *J* = 8.7 Hz, 1H), 1.58 (s, 3H), 0.35 (s, 3H). **^{13}C NMR (101 MHz, Chloroform-*d*) :** Many signals due to C-P and C-F coupling **^{19}F NMR (376 MHz, Chloroform-*d*) :** δ = -113.9, -114.3, -115.1, -115.2. **^{31}P NMR (162 MHz, Chloroform-*d*) :** δ = 156.9. **Optical rotation :** $[\alpha]_D^{20}$ = -72.5° (c = 1.0, $CHCl_3$) **HRMS** (ESI): Calculated for $C_{37}H_{29}F_4NaO_4P$ ($[M+Na]^+$): 667.1632; found: 667.1643

(3a*R*,8a*R*)-2,2-Dimethyl-6-phenyl-4,4,8,8-tetra-*p*-tolyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 4.16d

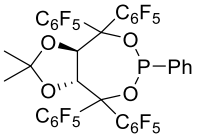


Chemical Formula: $C_{41}H_{41}O_4P$
Exact Mass: 628.27425

Following general procedure "Phosphonite", **4.16d** was obtained as a white solid (170 mg, 0.27 mmol, 90 %).

^{1}H NMR (400 MHz, Chloroform-*d*) : δ = 7.88 – 7.81 (m, 2H), 7.78 – 7.72 (m, 2H), 7.51 – 7.44 (m, 4H), 7.37 – 7.30 (m, 4H), 7.19 – 6.99 (m, 9H), 5.58 (dd, *J* = 8.7, 4.7 Hz, 1H), 4.77 (d, *J* = 8.6 Hz, 1H), 2.35 – 2.23 (m, 12H), 1.53 (s, 3H), 0.24 (s, 3H). **^{13}C NMR (101 MHz, Chloroform-*d*) :** δ = 144.3, 143.5 (d, $J_{C,P}$ = 3.7 Hz), 141.6 (d, $J_{C,P}$ = 10.9 Hz), 139.1 – 139.0 (m), 138.9 (d, $J_{C,P}$ = 1.9 Hz), 137.2 (d, $J_{C,P}$ = 10.6 Hz), 136.8 (d, $J_{C,P}$ = 5.5 Hz), 130.7, 130.1, 129.9, 129.4, 128.9, 128.8, 128.6, 128.6, 128.5, 128.4, 128.0, 127.4, 127.4, 111.3, 84.2 (d, $J_{C,P}$ = 3.4 Hz), 83.2 (d, $J_{C,P}$ = 7.6 Hz), 82.8 (d, $J_{C,P}$ = 23.5 Hz), 82.2 (d, $J_{C,P}$ = 4.5 Hz), 28.0, 25.0, 21.3, 21.2, 21.2, 21.1. **^{31}P NMR (162 MHz, Chloroform-*d*) :** δ = 155.6. **Optical rotation :** $[\alpha]_D^{20}$ = +58.4° (c = 1.06, $CHCl_3$). **HRMS** (ESI): Calculated for $C_{41}H_{41}O_4P$ ($[M+H]^+$): 629.2815; found: 629.2807

(3a*R*,8a*R*)-2,2-Dimethyl-4,4,8,8-tetrakis(perfluorophenyl)-6-phenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 4.16e

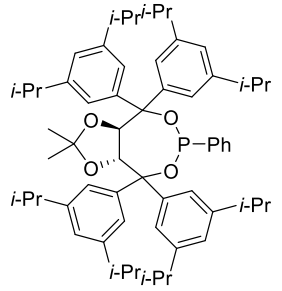


Chemical Formula: $C_{37}H_{13}F_{20}O_4P$
Exact Mass: 932.02321

Following general procedure "Phosphonite", **4.16e** was obtained as a white solid (221 mg, 0.237 mmol, 79 %).

^{1}H NMR (400 MHz, Chloroform-*d*) : δ = 7.65 – 7.58 (m, 2H), 7.43 – 7.35 (m, 3H), 5.90 (d, *J* = 8.2 Hz, 1H), 5.68 (d, *J* = 8.2 Hz, 1H), 1.07 (s, 3H), 0.82 (s, 3H). **^{13}C NMR (101 MHz, Chloroform-*d*) :** Many signals due to C-P and C-F coupling. **^{19}F NMR (376 MHz, Chloroform-*d*) :** δ = -131.0 – -131.2 (m), -134.4 – -134.9 (m), -138.0 – -138.5 (m), -139.3 – -139.9 (m), -150.5 – -150.9 (m), -151.3 – -151.7 (m), -151.9 – -152.1 (m), -152.5 – -152.7 (m), -160.0 – -160.2 (m), -160.7 – -160.9 (m), -161.0 – -161.3 (m), -161.4 – -161.8 (m). **^{31}P NMR (162 MHz, Chloroform-*d*) :** δ = 155.8. **Optical rotation :** $[\alpha]_D^{20}$ = -94.5° (c = 1.0, $CHCl_3$) **HRMS** (ESI): Calculated for $C_{37}H_{13}F_{20}O_4P$ ($[M+H]^+$): 933.0305; found: 933.0303

(3a*R*,8a*R*)-4,4,8,8-Tetrakis(3,5-diisopropylphenyl)-2,2-dimethyl-6-phenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 4.16f

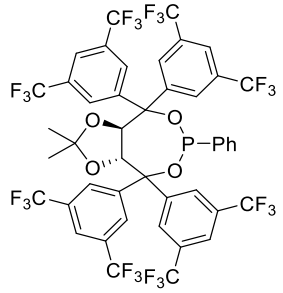


Chemical Formula: $C_{61}H_{81}O_4P$
Exact Mass: 908.58725

Following general procedure "Phosphonite", **L6** was obtained as a white solid (229 mg, 0.254 mmol, 84 %).

^{1}H NMR (400 MHz, Chloroform-*d*) : δ = 7.80 – 7.75 (m, 2H), 7.42 – 7.39 (m, 2H), 7.34 – 7.30 (m, 3H), 7.23 – 7.20 (m, 2H), 7.11 – 7.06 (m, 2H), 6.89 – 6.74 (m, 6H), 5.47 (dd, *J* = 8.6, 4.2 Hz, 1H), 4.80 (d, *J* = 8.6 Hz, 1H), 2.74 – 2.67 (m, 8H), 1.40 (s, 3H), 1.09 – 1.01 (m, 48H), 0.00 (s, 3H). **^{13}C NMR (101 MHz, Chloroform-*d*) :** δ = 148.1 (d, $J_{C,P}$ = 14.1 Hz), 147.3 (d, $J_{C,P}$ = 17.7 Hz), 146.9, 146.5 (d, $J_{C,P}$ = 4.2 Hz), 142.3 (d, $J_{C,P}$ = 12.1 Hz), 141.8 (d, $J_{C,P}$ = 1.8 Hz), 141.6 (d, $J_{C,P}$ = 1.9 Hz), 130.6, 130.2, 130.0, 128.4, 128.3, 125.2, 125.0, 124.9, 123.7, 123.7, 123.6, 123.5, 123.3, 110.6, 84.5 (d, $J_{C,P}$ = 4.4 Hz), 84.0 (d, $J_{C,P}$ = 7.1 Hz), 83.5 (d, $J_{C,P}$ = 21.6 Hz), 83.0 (d, $J_{C,P}$ = 4.7 Hz), 34.6, 34.3, 34.3, 34.2, 28.2, 24.4, 24.3, 24.2, 24.2, 24.1, 24.0.**^{31}P NMR (162 MHz, Chloroform-*d*) :** δ = 155.46. **Optical rotation :** $[\alpha]_D^{20}$ = +16.2° (c = 1.0, $CHCl_3$)

(3a*R*,8a*R*)-4,4,8,8-Tetrakis(3,5-bis(trifluoromethyl)phenyl)-2,2-dimethyl-6-phenyltetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine 4.16g

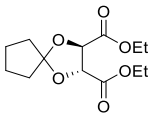


Chemical Formula: $C_{45}H_{25}F_{24}O_4P$
Exact Mass: 1116.11072

Following general procedure "Phosphonite", **4.16g** was obtained as a yellow solid (271 mg, 0.243 mmol, 81 %).

^{1}H NMR (400 MHz, Chloroform-*d*) : δ = 8.35 – 8.31 (m, 2H), 8.05 – 8.00 (m, 2H), 7.94 – 7.78 (m, 10H), 7.68 – 7.62 (m, 3H), 5.39 (dd, *J* = 8.8, 4.6 Hz, 1H), 4.48 (d, *J* = 8.7 Hz, 1H), 1.65 (s, 3H), 0.34 (s, 3H). **^{13}C NMR (101 MHz, Chloroform-*d*) :** Many signals due to C-P and C-F coupling. **^{19}F NMR (376 MHz, Chloroform-*d*) :** δ = -63.1, -63.15, -63.21, -63.22. **^{31}P NMR (162 MHz, Chloroform-*d*) :** δ = 161.8. **HRMS** (ESI): Calculated for $C_{45}H_{26}F_{24}O_4P$ ($[M+H]^+$): 1117.1185; found: 1117.1180

Diethyl (2*R*,3*R*)-1,4-dioxaspiro[4.4]nonane-2,3-dicarboxylate 4.18

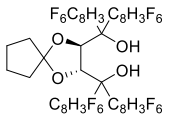


Chemical Formula: $C_{13}H_{20}O_6$
Exact Mass: 272.1260

To a solution of (+)-diethyl L-tartrate (8.33 mL, 48.5 mmol, 1 equiv) in toluene (50 mL) equipped with a Dean-Stark apparatus was added cyclopentanone (5.15 mL, 58.2 mmol, 1.2 equiv) and *p*-toluenesulfonic acid monohydrate (0,923 g, 4.85 mmol, 0.1 equiv). The reaction mixture was heated at 140°C until no evolution of water was observed. The reaction mixture was extracted with ethyl acetate, dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by silica gel chromatography to afford **4.18** (2.2 g, 8.1 mmol, 17%) as a colorless oil.

^{1}H NMR (400 MHz, Chloroform-*d*) : δ = 4.73 (s, 2H), 4.27 (q, J = 7.1 Hz, 4H), 2.02 – 1.95 (m, 2H), 1.90 – 1.83 (m, 2H), 1.81 – 1.78 (m, 1H), 1.73 – 1.68 (m, 3H), 1.32 (t, J = 7.1 Hz, 6H).

((2R,3R)-1,4-dioxaspiro[4.4]nonane-2,3-diyl)bis(bis(3,5-bis(trifluoromethyl)phenyl)methanol) 4.16h

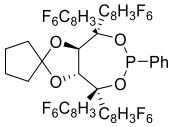


Chemical Formula: $C_{41}H_{24}F_{24}O_4$
Exact Mass: 1036.1291

Following general procedure "TADDOL", the Grignard reagent generated from 3,5-bis(trifluoromethyl)bromobenzene (3.22 g, 11 mmol, 5.0 equiv) and magnesium (283 mg, 11.7 mmol, 5.3 equiv) in THF was reacted with Diethyl (2*R*,3*R*)-1,4-dioxaspiro[4.4]nonane-2,3-dicarboxylate **4.18** (600 mg, 2.2 mmol, 1.0 equiv). The crude mixture was purified by flash chromatography affording **4.16h** (1,75 g, 1.68 mmol, 77%) as a yellow oil which solidified under vacuum.

^{1}H NMR (400 MHz, Chloroform-*d*) : δ = 8.05 (s, 4H), 7.94 (s, 2H), 7.84 (s, 6H), 4.94 (s, 2H), 4.28 (s, 2H), 1.73 – 1.39 (m, 8H). **^{13}C NMR (101 MHz, Chloroform-*d*) :** δ =145.9, 143.6, 132.32 (q, $J_{C,F}$ = 33.7 Hz), 131.87 (q, $J_{C,F}$ = 33.7 Hz), 128.23 (m), 127.55 (m), 123.3 (q, $J_{C,F}$ = 273 Hz), 123.1 (q, $J_{C,F}$ = 273 Hz), 122.80 (m), 120.9, 81.2, 77.4, 77.1, 36.8, 22.6.**^{19}F NMR (376 MHz, Chloroform-*d*) :** -63.06, -63.19.

(3a'R,8a'R)-4',4',8',8'-tetrakis(3,5-bis(trifluoromethyl)phenyl)-6'-phenyltetrahydrospiro[cyclopentane-1,2'-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepine] 4.17h



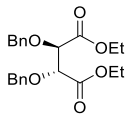
Chemical Formula: $C_{47}H_{27}F_{24}O_4P$
Exact Mass: 1142.1264

Following general procedure "Phosphonite", **4.17h** was obtained as a yellow solid (300 mg, 0.271 mmol, 91 %).

^{1}H NMR (400 MHz, Chloroform-*d*) : δ = 8.30 – 8.28 (m, 2H), 8.02 – 8.00 (m, 2H), 7.90 – 7.88 (m, 3H), 7.88 – 7.86 (m, 2H), 7.85 – 7.84 (m, 3H), 7.83 – 7.76 (m, 2H), 7.71 – 7.61 (m, 2H), 5.42 (dd, J = 8.7, 4.8 Hz, 1H), 4.38 (d, J = 8.7 Hz, 1H), 2.28 – 2.17 (m, 1H), 2.13 – 2.00 (m, 1H), 1.76 – 1.62 (m, 2H), 1.50 – 1.37 (m, 1H), 1.33 – 1.27 (m, 1H), 0.57 – 0.45 (m, 1H), 0.39 – 0.25 (m, 1H).

^{13}C NMR (101 MHz, Chloroform-*d*) : Many signals due to C-P and C-F coupling. **^{19}F NMR (376 MHz, Chloroform-*d*) :** δ = -63.1, -63.1, -63.1, -63.2. **^{31}P NMR (162 MHz, Chloroform-*d*) :** δ = 161.67.

Diethyl (2*R*,3*R*)-2,3-bis(benzyloxy)succinate 4.19

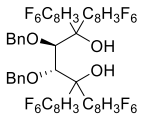


Chemical Formula: $C_{22}H_{26}O_6$
Exact Mass: 386.1729

To a stirred suspension of NaH 60% (400 mg, 9.98 mmol, 2 equiv) in DMF (12 mL) at 0°C were added dropwise a solution of (+)-diethyl L-tartrate (0.857 mL, 4.99 mmol, 1 equiv) in DMF (3 mL). The resulting mixture was stirred during two hours at 0°C, then benzyl bromide (1.8 mL, 15 mmol, 3 equiv) was added to the reaction mixture and the reaction was stirred for two hours at room temperature. The reaction was quenched with sat. $NaHCO_3$ and extracted with diethyl ether. The combined organic layers were washed with water, dried over $MgSO_4$, filtered and concentrated under reduce pressure. The crude mixture was purified by silica gel chromatography to afford **4.19** (750 mg, 1,941 mmol, 39%) as a colorless oil.

^{1}H NMR (400 MHz, Chloroform-*d*) : δ = 7.32 – 7.27 (m, 2H), 7.25 – 7.19 (m, 3H), 4.84 (d, J = 12.0 Hz, 2H), 4.42 (d, J = 12.0 Hz, 2H), 4.36 (s, 2H), 4.21 – 4.12 (m, 2H), 4.03 (m, 2H), 1.14 (t, J = 7.2 Hz, 6H).

(2*R*,3*R*)-2,3-bis(benzyloxy)-1,1,4,4-tetrakis(3,5-bis(trifluoromethyl)phenyl)butane-1,4-diol 4.16i

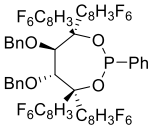


Chemical Formula: $C_{50}H_{30}F_{24}O_4$
Exact Mass: 1150.1761

Following general procedure "TADDOL", the Grignard reagent generated from 3,5-bis(trifluoromethyl)bromobenzene (2.27 g, 7.75 mmol, 5.0 equiv) and magnesium (200 mg, 8.22 mmol, 5.3 equiv) in THF was reacted with diethyl (2*R*,3*R*)-2,3-bis(benzyloxy)succinate **4.19** (600 mg, 1.55 mmol, 1.0 equiv). The crude mixture was purified by flash chromatography affording **4.16i** (240 mg, 0,21 mmol, 14%) as a yellow oil which solidified under vacuum.

^{1}H NMR (400 MHz, Chloroform-*d*) : δ = 8.17 (s, 4H), 8.03 – 7.92 (m, 4H), 7.92 – 7.86 (m, 4H), 7.27 – 7.11 (m, 6H), 6.72 – 6.53 (m, 4H), 4.62 (s, 4H), 3.62 – 3.57 (m, 2H), 3.42 – 3.35 (m, 2H). **^{13}C NMR (101 MHz, Chloroform-*d*) :** 147.0, 144.3, 135.7, 132.6 (q, $J_{C,F}$ = 33.9 Hz), 131.9 (q, $J_{C,F}$ = 33.6 Hz), 128.62, 128.43, 128.22 (m), 127.29, 127.07 (m), 122.74 (m), 123.2 (q, $J_{C,F}$ = 273 Hz), 123.1 (q, $J_{C,F}$ = 273 Hz), 122.47 (m), 81.0, 78.7, 77.4, 74.7. **^{19}F NMR (376 MHz, Chloroform-*d*) :** δ = -63.13, -63.17.

(5*R*,6*R*)-5,6-bis(benzyloxy)-4,4,7,7-tetrakis(3,5-bis(trifluoromethyl)phenyl)-2-phenyl-1,3,2-dioxaphosphepane 4.17i

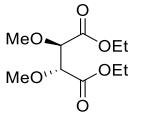


Chemical Formula: $C_{56}H_{33}F_{24}O_4P$
Exact Mass: 1256.1733

Following general procedure "Phosphonite", **4.17i** was obtained as a yellow solid (180 mg, 0.148 mmol, 92 %).

^{1}H NMR (400 MHz, Chloroform-*d*) : δ = 8.43 – 8.36 (m, 2H), 8.19 – 8.14 (m, 2H), 8.10 – 8.03 (m, 1H), 7.99 – 7.94 (m, 1H), 7.89 – 7.85 (m, 3H), 7.80 – 7.71 (m, 2H), 7.67 – 7.64 (m, 2H), 7.62 – 7.53 (m, 4H), 7.37 – 7.30 (m, 3H), 7.15 – 6.97 (m, 5H), 6.46 – 6.19 (m, 2H), 5.28 (d, J = 10.5 Hz, 1H), 5.10 (dd, J = 7.8, 5.1 Hz, 1H), 4.45 (d, J = 10.7 Hz, 1H), 4.37 (d, J = 7.8 Hz, 1H), 4.01 (d, J = 11.1 Hz, 1H), 3.27 (d, J = 11.1 Hz, 1H). **^{13}C NMR (101 MHz, Chloroform-*d*) :** Many signals due to C-P and C-F coupling. **^{19}F NMR (376 MHz, Chloroform-*d*) :** δ = -62.9, -63.0, -63.0, -63.2.

Diethyl (2*R*,3*R*)-2,3-dimethoxysuccinate 4.20



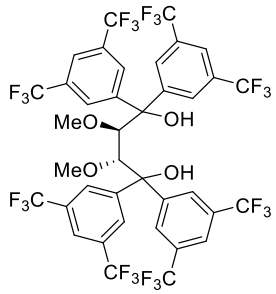
Chemical Formula: $C_{10}H_{18}O_6$
Exact Mass: 234.11034

To a stirred suspension of NaH 60% (2 g, 50 mmol, 2 equiv) in diethyl ether (250 mL) at 0°C were added (+)-diethyl L-tartrate (4.13 mL, 25 mmol, 1 equiv) and dimethyl sulfate (4.91 mL, 51.2 mmol, 2.05 equiv). The resulting mixture was stirred overnight at room temperature. The reaction was quenched with sat. $NaHCO_3$, the aqueous phase extracted with diethyl ether. The combined organic layers were washed with water, dried over $MgSO_4$, filtered and concentrated

under reduce pressure. The crude mixture was purified by silica gel chromatography to afford **4.20** (4.976 g, 21.242 mmol, 85%) as a colorless oil.

^{1}H NMR (400 MHz, Chloroform-*d*) : δ = 4.33-4.19 (m, 4H), 4.21 (s, 2H,), 3.45 (s, 6H), 1.30 (t, J = 7.2 Hz, 6 H).

(2*R*,3*R*)-1,1,4,4-Tetrakis(3,5-bis(trifluoromethyl)phenyl)-2,3-*d*imethoxybutane-1,4-diol 4.16j

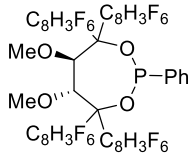


Chemical Formula: $C_{38}H_{22}F_{24}O_4$
Exact Mass: 998.11349

Following general procedure "TADDOL", the Grignard reagent generated from 3,5-bis(trifluoromethyl)bromobenzene (12.5 g, 42.7 mmol, 5.0 equiv) and magnesium (1.1 g, 45.3 mmol, 5.3 equiv) in THF was reacted with diethyl (2*R*,3*R*)-2,3-dimethoxysuccinate (2 g, 8.54 mmol, 1.0 equiv). The crude mixture was purified by flash chromatography affording 6.3 g (6.31 mmol, 74%) of a yellow oil which solidified under vacuum.

^{1}H NMR (400 MHz, Chloroform-*d*) : δ = 8.11 – 8.06 (m, 4H), 7.95 – 7.91 (m, 4H), 7.92 – 7.90 (m, 2H), 7.86 – 7.84 (m, 5H), 4.42 (s, 2H), 4.23 (s, 2H), 2.46 (s, 6H). **^{13}C NMR (101 MHz, Chloroform-*d*) :** δ = 146.72, 144.93, 132.71 (q, $J_{C,F}$ = 33.7 Hz), 132.07 (q, $J_{C,F}$ = 33.6 Hz), 127.39 – 127.16 (m), 126.77 – 126.46 (m), 123.2 (q, $J_{C,F}$ = 273 Hz), 123.1 (q, $J_{C,F}$ = 273 Hz), 122.47 (m), 122.42 – 122.21 (m), 84.21, 78.77, 60.66. **^{19}F NMR (376 MHz, Chloroform-*d*) :** δ = -63.12, -63.24. **IR (neat):** ν = 3290, 2884, 1625, 1460, 1365, 1005, 762 cm^{-1}. **HRMS** (ESI): Calculated for $C_{38}H_{22}F_{24}O_4$ ($[M-H]^-$): 997.1077; found: 997.1062. **Optical rotation :** $[\alpha]_D^{20}$ = -1° (c = 1.0, $CHCl_3$)

(5*R*,6*R*)-4,4,7,7-Tetrakis(3,5-bis(trifluoromethyl)phenyl)-5,6-dimethoxy-2-phenyl-1,3,2-dioxaphosphepane 4.17j

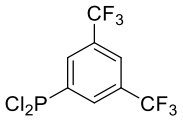


Chemical Formula: $C_{44}H_{25}F_{24}O_4P$
Exact Mass: 1104.11072

Following general procedure "Phosphonite", **4.17j** was obtained as a yellow solid (292 mg, 0.264 mmol, 88 %).

^{1}H NMR (400 MHz, Chloroform-*d*) : δ = 8.28 – 8.25 (m, 2H), 8.07 – 8.06 (m, 2H), 8.01 – 7.98 (m, 1H), 7.89 (s, 1H), 7.88 (s, 1H), 7.85 (s, 2H), 7.79 (s, 1H), 7.77 – 7.71 (m, 2H), 7.69 (s, 2H), 7.63 – 7.53 (m, 3H), 4.73 (dd, *J* = 7.9, 5.0 Hz, 1H), 3.86 (d, *J* = 7.9 Hz, 1H), 3.65 (s, 3H), 2.55 (s, 3H). **^{13}C NMR (101 MHz, Chloroform-*d*) :** Many signals due to C-P and C-F coupling. **^{19}F NMR (376 MHz, Chloroform-*d*) :** δ = -62.9, -63.0, -63.1, -63.2. **^{31}P NMR (162 MHz, Chloroform-*d*) :** δ = 160.0. **Optical rotation :** $[\alpha]_D^{20}$ = -36.0° (c = 1.01, $CHCl_3$). **HRMS** (ESI): Calculated for $C_{44}H_{26}F_{24}O_4P$ ($[M+H]^+$): 1105.1180; found: 1105.1173

Dichloro(3,5-bis(trifluoromethyl)phenyl)phosphine 4.20a

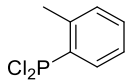


Chemical Formula: $C_8H_3Cl_2F_6P$
Exact Mass: 313.92536

Following general procedure "Dichloroarylphosphine", the aryl lithium reagent generated from 3,5- bis(trifluoromethyl)bromobenzene (6.16 g, 21.00 mmol, 1.0 equiv) and *n*butyl lithium (2.13 M, 9.86 mL, 21.00 mmol, 1.0 equiv) in Et_2O was reacted with $(Et_2N)_2PCl$ (4.87 g, 4.87 mL, 23.10 mmol, 1.1 equiv) and hydrogen chloride (2 M, 47.30 mL, 94.50 mmol, 4.5 equiv) in Et_2O (47 mL). The crude mixture was purified by distillation under reduced pressure (6 x 10^{-2} mbar, 35-45°C) affording 3.34 g (10.50 mmol, 50%) of a colorless oil.

^{31}P{1H} NMR (Chloroform-*d*, 162 MHz) : δ = 151.5 ppm. **^{19}F{1H} NMR (Chloroform-*d*, 376 MHz) :** δ = -63.0 ppm. The physical and spectroscopic properties matched those described in the literature[61].

Dichloro(*o*-tolyl)phosphine 4.20b

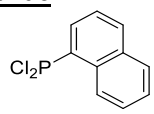


Chemical Formula: $C_7H_7Cl_2P$
Exact Mass: 191.96624

Following general procedure "Dichloroarylphosphine", the Grignard reagent formed from 2-bromotoluene (3.83 mL, 31.8 mmol, 1.5 equiv) and magnesium (0.77 g, 31.8 mmol, 1.5 equiv) was reacted with $(Et_2N)_2PCl$ (4.47 g, 21.2 mmol, 1.0 equiv) and HCl (2 M, 53 mL, 106.00 mmol, 5 equiv) in Et_2O (45 mL). The crude mixture was purified by distillation under reduced pressure ($6x10^{-2}$ mbar, 55-60°C) affording 2.05 g (10.6 mmol, 50%) of a colorless oil.

$^{31}P\{1H\}$ NMR (Chloroform-*d*, 162 MHz) : δ = 163.3 ppm. The physical and spectroscopic properties matched those described in the literature[61].

Dichloro(naphthalen-1-yl)phosphine 4.20c

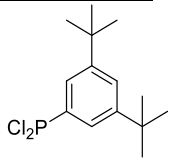


Chemical Formula: $C_{10}H_7Cl_2P$
Exact Mass: 227.96624

Following general procedure "Dichloroarylphosphine", the Grignard reagent formed from 1-bromo-naphtalene (4.35 g, 21.0 mmol, 1.1 equiv) and magnesium (0.51 g, 21 mmol, 1.1 equiv) was reacted with $(Et_2N)_2PCl$ (4.0 g, 19.1 mmol, 1.0 equiv) and HCl (2 M, 47.8 mL, 95.5 mmol, 5 equiv) in Et_2O (40 mL). The crude mixture was purified by distillation under reduced pressure (10^{-1} mbar, 100-105°C) affording 2.85 g (12.4 mmol, 65%) of a colorless oil.

$^{31}P\{1H\}$ NMR (Chloroform-*d*, 162 MHz) : δ = 162.8 ppm. The physical and spectroscopic properties matched those described in the literature[194].

Dichloro(3,5-di-*tert*-butylphenyl)phosphine 4.20d

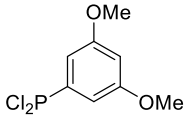


Chemical Formula: $C_{14}H_{21}Cl_2P$
Exact Mass: 290.07579

Following general procedure "Dichloroarylphosphine", the Grignard reagent formed from 1-bromo-3,5-di-*tert*-butylbenzene (5.65 g, 21.0 mmol, 1.1 equiv) and magnesium (0.51 g, 21 mmol, 1.1 equiv) was reacted with $(Et_2N)_2PCl$ (4.0 g, 19.1 mmol, 1.0 equiv) and HCl (2 M, 47.8 mL, 95.5 mmol, 5 equiv) in Et_2O (40 mL). The crude mixture was purified by distillation under reduced pressure ($4x10^{-1}$ mbar, 105-110°C) affording 1.1 g (3.78 mmol, 20%) of a colorless oil.

^{31}P{1H} NMR (Chloroform-*d*, 162 MHz) : δ = 164.0 ppm. The physical and spectroscopic properties matched those described in the literature[195].

Dichloro(3,5-*di*methoxyphenyl)phosphine 4.20e

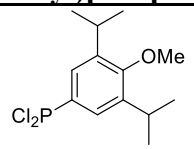


Chemical Formula: $C_8H_9Cl_2O_2P$
Exact Mass: 237.97172

Following general procedure "Dichloroarylphosphine", the aryl lithium reagent generated from 1-bromo-3,5-dimethoxybenzene (5.00 mg, 23.00 mmol, 1.0 equiv) and *n*-butyllithium (2 M, 11.5 mL, 23.00 mmol, 1.0 equiv) in Et_2O at -78 °C was reacted with $(Et_2N)_2PCl$ (5.34 g, 25.30 mmol, 1.1 equiv) and hydrogen chloride (2 M, 0.052 mL, 103.00 mmol, 4.5 equiv) in Et_2O (52 mL). The crude mixture was purified by distillation under reduced pressure (3 x 10^{-3} mbar, 104-106 °C) affording 2.17 g (8.98 mmol, 39%) of a colorless oil.

^{31}P{1H} NMR (Chloroform-*d*, 162 MHz) : δ = 160.9 ppm. The physical and spectroscopic properties matched those described in the literature[61].

Dichloro(3,5-diisopropyl-4-methoxyphenyl)phosphine 4.20f

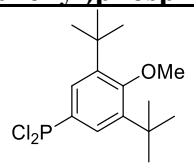


Chemical Formula: $C_{13}H_{19}Cl_2OP$
Exact Mass: 292.05506

Following general procedure Dichloroarylphosphine, the aryl lithium reagent generated from 5-bromo-1,3-diisopropyl-2-methoxybenzene (5.0 g, 16.7 mmol, 1.0 equiv) and *n*-butyllithium (2 M, 11.5 mL, 16.7 mmol, 1.0 equiv) in Et_2O at -78 °C was reacted with $(Et_2N)_2PCl$ (3.5 g, 16.7 mmol, 1.0 equiv) and hydrogen chloride (2 M, 47.7 mL, 83.5 mmol, 5 equiv) in Et_2O (35 mL). The crude mixture was purified by distillation under reduced pressure (4 x 10^{-1} mbar, 110°C) affording 2.0 g (6.8 mmol, 41%) of a colorless oil.

^{31}P{1H} NMR (Chloroform-*d*, 162 MHz) : δ = 162.9 ppm.

Dichloro(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphine 4.20g



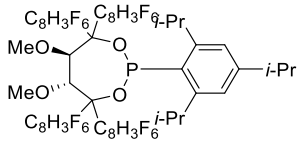
Chemical Formula: $C_{15}H_{23}Cl_2OP$
Exact Mass: 320.08636

Following general procedure "Dichloroarylphosphine", the aryl lithium reagent generated from 5-bromo-1,3-di-tert-butyl-2-methoxybenzene (4.5 g, 16.7 mmol, 1.0 equiv) and *n*-butyllithium

(2 M, 11.5 mL, 16.7 mmol, 1.0 equiv) in Et_2O at -78 °C was reacted with $(Et_2N)_2PCl$ (3.5 g, 16.7 mmol, 1.0 equiv) and hydrogen chloride (2 M, 47.7 mL, 83.5 mmol, 5 equiv) in Et_2O (35 mL). The crude mixture was purified by distillation under reduced pressure (4 x 10^{-1} mbar, 120°C) affording 2.7 g (8.4 mmol, 50%) of a colorless oil.

^{31}P{1H} NMR (Chloroform-*d*, 162 MHz) : δ = 164.2 ppm. The physical and spectroscopic properties matched those described in the literature[196].

(5*R*,6*R*)-4,4,7,7-Tetrakis(3,5-bis(trifluoromethyl)phenyl)-5,6-dimethoxy-2-(2,4,6-triisopropylphenyl)-1,3,2-dioxaphosphepane 4.17k

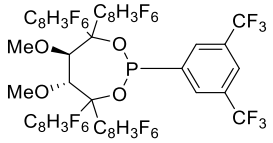


Chemical Formula: $C_{53}H_{43}F_{24}O_4P$
Exact Mass: 1230.25157

Following general procedure "Phosphonite", **4.17k** was obtained as a yellow solid (221 mg, 0.18 mmol, 60%).

^{1}H NMR (400 MHz, Chloroform-*d*) : δ = 8.39 – 8.36 (m, 2H), 8.09 – 8.02 (m, 2H), 7.95 – 7.92 (m, 2H), 7.91 – 7.88 (m, 1H), 7.84 – 7.82 (m, 1H), 7.82 – 7.80 (m, 1H), 7.72 – 7.70 (m, 2H), 7.62 – 7.60 (m, 2H), 7.09 (d, *J* = 3.2 Hz, 2H), 4.94 (dd, *J* = 7.9, 6.3 Hz, 1H), 4.10 (d, *J* = 7.9 Hz, 1H), 3.86 (s, 2H), 3.70 (s, 3H), 2.89 (hept, *J* = 7.0 Hz, 1H), 2.44 (s, 3H), 1.31 – 1.21 (m, 18H). **^{13}C NMR (101 MHz, Chloroform-*d*) :** Many signals due to C-P and C-F coupling **^{19}F NMR (235 MHz, Chloroform-*d*) :** δ = -62.84, -62.88, -62.90, -63.13. **^{31}P NMR (162 MHz, Chloroform-*d*) :** δ = 172.9. **Optical rotation :** $[\alpha]_D^{20}$ = -8.0° (c = 1.02, $CHCl_3$) **HRMS** (ESI): Calculated for $C_{53}H_{44}F_{24}O4P$ ($[M+H]^+$): 1231.2588; found: 1231.2592

(5*R*,6*R*)-2,4,4,7,7-Pentakis(3,5-bis(trifluoromethyl)phenyl)-5,6-dimethoxy-1,3,2-dioxaphosphepane 4.17l

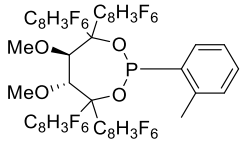


Chemical Formula: $C_{46}H_{23}F_{30}O_4P$
Exact Mass: 1240.08549

Following general procedure "Phosphonite", **4.17l** was obtained as a yellow solid (265 mg, 0.214 mmol, 81 %).

^{1}H NMR (400 MHz, Chloroform-*d*) : δ = 8.24 – 8.20 (m, 2H), 8.18 – 8.15 (m, 1H), 8.15 – 8.14 (m, 1H), 8.09 – 8.08 (m, 1H), 8.03 – 8.01 (m, 1H), 8.01 – 7.97 (m, 2H), 7.94 – 7.92 (m, 1H), 7.92 – 7.89 (m,1H), 7.84 – 7.79 (m, 2H), 7.68 – 7.64 (m, 2H), 4.79 – 4.72 (m, 1H), 3.98 (d, *J* = 7.7 Hz, 1H), 3.63 (s, 3H), 2.60 (s, 3H). **^{13}C NMR (101 MHz, Chloroform-*d*) :** Many signals due to C-P and C-F coupling. **^{31}P NMR (162 MHz, Chloroform-*d*) :** δ = 153.7. **^{19}F NMR (376 MHz, Chloroform-*d*) :** δ = -63.09, -63.19, -63.38, -63.47, -63.52. **Optical rotation :** $[\alpha]_D^{20}$ = -32.6° (c = 1.03, $CHCl_3$). **HRMS** (ESI): Calculated for $C_{46}H_{24}F_{30}O_4P$ ($[M+H]^+$): 1241.0928; found: 1241.0929

(5*R*,6*R*)-4,4,7,7-Tetrakis(3,5-bis(trifluoromethyl)phenyl)-5,6-dimethoxy-2-(o-tolyl)-1,3,2-dioxaphosphepane 4.17m

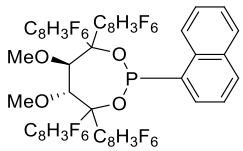


Chemical Formula: $C_{45}H_{27}F_{24}O_4P$
Exact Mass: 1118.12637

Following general procedure "Phosphonite", **4.17m** was obtained as a yellow solid (302 mg, 0.27 mmol, 90 %).

^{1}H NMR (400 MHz, Chloroform-*d*) : δ = 8.26 – 8.21 (m, 2H), 8.07 – 8.02 (m, 2H), 7.94 – 7.89 (m, 2H), 7.82 – 7.78 (m, 2H), 7.77 – 7.74 (m, 2H), 7.72 – 7.70 (m, 1H), 7.67 – 7.63 (m, 2H), 7.44 – 7.32 (m, 2H), 7.20 – 7.13 (m, 1H), 4.71 (dd, *J* = 7.9, 5.3 Hz, 1H), 3.73 (d, *J* = 8.0 Hz, 1H), 3.61 (s, 3H), 2.48 (s, 3H), 2.31 (s, 3H). **^{13}C NMR (101 MHz, Chloroform-*d*) :** Many signals due to C-P and C-F coupling. **^{31}P NMR (162 MHz, Chloroform-*d*) :** δ = 157.5. **^{19}F NMR (376 MHz, Chloroform-*d*) :** δ = -62.94, -63.05, -63.20, -63.24. **Optical rotation :** $[\alpha]_D^{20}$ = -27.1° (c = 1.0, $CHCl_3$). **HRMS** (ESI): Calculated for $C_{45}H_{28}F_{24}O_4P$ ($[M+H]^+$): 1119.1336; found: 1119.1332

(5*R*,6*R*)-4,4,7,7-Tetrakis(3,5-bis(trifluoromethyl)phenyl)-5,6-dimethoxy-2-(naphthalen-1-yl)-1,3,2-dioxaphosphepane 4.17n

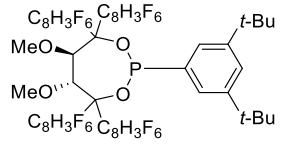


Chemical Formula: $C_{48}H_{27}F_{24}O_4P$
Exact Mass: 1154.12637

Following general procedure "Phosphonite", **4.17n** was obtained as a yellow solid (280 mg, 0.243 mmol, 81 %).

^{1}H NMR (400 MHz, Chloroform-*d*) : δ = 8.56 – 8.49 (m, 1H), 8.30 – 8.24 (m, 2H), 8.13 – 8.07 (m, 2H), 8.04 – 7.87 (m, 4H), 7.81 – 7.74 (m, 4H), 7.71 – 7.62 (m, 3H), 7.60 – 7.53 (m, 3H), 4.79 (dd, *J* = 6.8 Hz, 1H), 3.83 (d, *J* = 8.0 Hz, 1H), 3.69 (s, 3H), 2.54 (s, 3H). **^{13}C NMR (101 MHz, Chloroform-*d*) :** Many signals due to C-P and C-F coupling. **^{19}F NMR (376 MHz, Chloroform-*d*) :** δ = -62.97, -63.08, -63.12, -63.15. **^{31}P NMR (162 MHz, Chloroform-*d*) :** δ = 165.7. **Optical rotation :** $[\alpha]_D^{20}$ = -23.7° (c = 1.02, $CHCl_3$). **HRMS** (ESI): Calculated for $C_{48}H_{28}F_{24}O_4P$ ($[M+H]^+$): 1155.1336; found: 1155.1320

(5*R*,6*R*)-4,4,7,7-Tetrakis(3,5-bis(trifluoromethyl)phenyl)-2-(3,5-di-tert-butylphenyl)-5,6-dimethoxy-1,3,2-dioxaphosphepane 4.17o

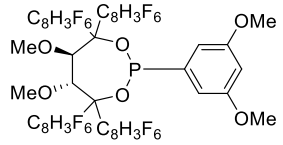


Chemical Formula: $C_{52}H_{41}F_{24}O_4P$
Exact Mass: 1216.23592

Following general procedure "Phosphonite", **4.17o** was obtained as a yellow solid (299 mg, 0.246 mmol, 82 %).

^{1}H NMR (400 MHz, Chloroform-*d*) : δ = 8.29 – 8.24 (m, 2H), 8.10 – 8.05 (m, 2H), 7.94 – 7.88 (m, 1H), 7.81 – 7.75 (m, 4H), 7.73 – 7.60 (m, 6H), 4.66 (dd, *J* = 8.0, 5.5 Hz, 1H), 3.67 (s, 3H), 3.64 (d, *J* = 8.0 Hz, 1H), 2.47 (s, 3H), 1.32 (s, 18H). **^{13}C NMR (101 MHz, Chloroform-*d*) :** Many signals due to C-P and C-F coupling. **^{19}F NMR (376 MHz, Chloroform-*d*) :** δ = -62.98, -63.01, -63.05, -63.12. **^{31}P NMR (162 MHz, Chloroform-*d*) :** δ = 161.4. **HRMS** (ESI): Calculated for $C_{52}H_{42}F_{24}O_4P$ ($[M+H]^+$): 1217.2437; found: 1217.2432

(5*R*,6*R*)-4,4,7,7-Tetrakis(3,5-bis(trifluoromethyl)phenyl)-2-(3,5-dimethoxyphenyl)-5,6-dimethoxy-1,3,2-dioxaphosphepane 4.17p



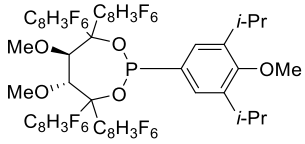
Chemical Formula: $C_{46}H_{29}F_{24}O_6P$
Exact Mass: 1164.13185

Following general procedure "Phosphonite", **4.17p** was obtained as a yellow solid (157 mg, 0.135 mmol, 45 %).

^{1}H NMR (400 MHz, Chloroform-*d*) : δ = 8.26 – 8.24 (m, 2H), 8.10 – 8.08 (m, 2H), 8.01 – 7.97 (m, 1H), 7.90 – 7.88 (m, 1H), 7.88 – 7.87 (m, 1H), 7.85 – 7.84 (m, 2H), 7.80 – 7.77 (m, 1H), 7.72 – 7.70 (m, 2H), 6.91 (d, *J* = 2.3 Hz, 1H), 6.88 (d, *J* = 2.3 Hz, 1H), 6.65 (t, *J* = 2.3 Hz, 1H), 4.72 (dd, *J* = 7.9, 4.9 Hz, 1H), 3.86 (s, 6H), 3.85 (d, *J* = 8.0 Hz, 1H), 3.65 (s, 3H), 2.56 (s, 3H). **^{13}C NMR (101 MHz, Chloroform-*d*) :** Many signals due to C-P and C-F coupling.

^{19}F NMR (376 MHz, Chloroform-*d*) : δ = -62.97, -63.08, -63.12, -63.15. **^{31}P NMR (162 MHz, Chloroform-*d*) :** δ = 158.8. **^{19}F NMR (376 MHz, Chloroform-*d*) :** δ = -62.93, -62.97, -63.10, -63.11. **Optical rotation :** $[\alpha]_D^{20}$ = -33.3° (c = 1.08, $CHCl_3$) **HRMS** (ESI): Calculated for $C_{46}H_{30}F_{24}O_6P$ ($[M+H]^+$): 1165.1391; found: 1165.1393

(5*R*,6*R*)-4,4,7,7-Tetrakis(3,5-bis(trifluoromethyl)phenyl)-2-(3,5-diisopropyl-4-methoxyphenyl)-5,6-dimethoxy-1,3,2-dioxaphosphepane 4.17q

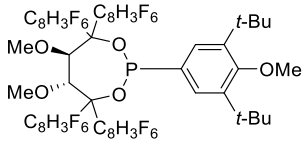


Chemical Formula: $C_{51}H_{39}F_{24}O_5P$
Exact Mass: 1218.21519

Following general procedure "Phosphonite", **4.17q** was obtained as a yellow solid (287 mg, 0.237 mmol, 79 %).

^{1}H NMR (400 MHz, Chloroform-*d*) : δ = 8.29 – 8.24 (m, 2H), 8.10 – 8.06 (m, 2H), 7.93 – 7.89 (m, 1H), 7.79 – 7.78 (m, 1H), 7.78 – 7.77 (m, 3H), 7.74 – 7.71 (m, 1H), 7.70 – 7.66 (m, 2H), 7.56 (s, 1H), 7.53 (s, 1H), 4.64 (dd, *J* = 8.0, 5.6 Hz, 1H), 3.75 (s, 3H), 3.68 (s, 3H), 3.61 (d, *J* = 8.0 Hz, 1H), 3.34 (hept, *J* = 6.9 Hz, 2H), 1.24 (d, *J* = 6.9 Hz, 6H), 1.21 (d, *J* = 6.9 Hz, 6H). **^{13}C NMR (101 MHz, Chloroform-*d*) :** Many signals due to C-P and C-F coupling. **^{31}P NMR (162 MHz, Chloroform-*d*) :** δ = 160.4. **^{19}F NMR (376 MHz, Chloroform-*d*) :** δ = -62.99, -63.01, -63.05, -63.12. **Optical rotation :** $[\alpha]_D^{20}$ = -21.2° (c = 1.0, $CHCl_3$). **HRMS** (ESI): Calculated for $C_1H_{40}F_{24}O_5P$ ($[M+H]^+$): 1219.2225; found: 1219.2234

(5*R*,6*R*)-4,4,7,7-Tetrakis(3,5-bis(trifluoromethyl)phenyl)-2-(3,5-di-tert-butyl-4-methoxyphenyl)-5,6-dimethoxy-1,3,2-dioxaphosphepane 4.17r



Chemical Formula: $C_{53}H_{43}F_{24}O_5P$
Exact Mass: 1246.24649

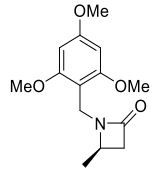
Following general procedure "Phosphonite", **4.17 r** was obtained as a yellow solid (310 mg, 0.249 mmol, 83 %).

^{1}H NMR (400 MHz, Chloroform-*d*) : δ = 8.29 – 8.25 (m, 2H), 8.10 – 8.05 (m, 2H), 7.94 – 7.91 (m, 1H), 7.81 – 7.80 (m, 1H), 7.79 – 7.77 (m, 2H), 7.75 – 7.73 (m, 1H), 7.72 – 7.67 (m, 3H), 7.19 (s, 2H), 4.64 (dd, *J* = 7.9, 5.6 Hz, 1H), 3.71 (s, 3H), 3.68 (s, 3H), 3.65 – 3.61 (m, 1H), 2.47 (s, 3H), 1.42 (s,9H), 1.34 (s, 9H). **^{13}C NMR (101 MHz, Chloroform-*d*) :** Many signals due to C-P and C-F coupling. **^{31}P NMR (162 MHz, Chloroform-*d*) :** δ = 161.3.

^{19}F NMR (376 MHz, Chloroform-*d*) : δ = -63.01, -63.05, -63.12. **Optical rotation :** $[\alpha]_D^{20}$ = -20.3° (c = 1.06, $CHCl_3$). **HRMS** (ESI): Calculated for $C_{53}H_{44}F_{24}O_5P$ ($[M+H]^+$): 1247.2538; found: 1247.2523

3.11. Enantioselective version and application

(*R*)-4-Methyl-1-(2,4,6-trimethoxybenzyl)azetidin-2-one 4.12a



Chemical Formula: $C_{14}H_{19}NO_4$
Exact Mass: 265.1314

Enantioselective reaction: CO atmosphere

Following general procedure B, Isopropyl(2,4,6-trimethoxybenzyl)carbamoyl chloride (400 mg, 1.33 mmol, 1 equiv) was reacted with $PdCl_2$ (24 mg, 0.133 mmol, 10 mol%), **L** ligand (332 mg , 0.266 mmol, 20 mol%), pivalic acid (41 mg, 0.4 mmol, 30 mol%) and cesium carbonate (650 mg, 2 mmol, 1.5 equiv) in mesitylene (26.2 mL), under CO atmosphere. The mixture was stirred for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent, to provide oil **2a** (266 mg, 1 mmol, 75 %, e.r.: 92:8).

Optical rotation : $[\alpha]_D^{20}$ = +71.8° (c = 1.0, $CHCl_3$)

Enantioselective reaction: Two-chamber system:

Following general procedure A, Chamber A was filled with $Pd(OAc)_2$ (8.9 mg, 0.04 mmol, 30 mol%), P(*t*-Bu)$_3$.HBF_4 (12 mg , 0.04 mmol, 30 mol%), COgen (97 mg, 0.4 mmol, 3.0 equiv), Cy_2NMe (161 mg, 0.798 mmol, 6.0 equiv) and mesitylene (0.5 mL). Chamber B, previously charged with isopropyl(2,4,6-trimethoxybenzyl)carbamoyl chloride (40 mg, 0.133 mmol, 1 equiv) was reacted with $PdCl_2$ (2.4 mg, 0.0133 mmol, 10 mol%), **L** ligand (33.2 mg , 0.0266 mmol, 20 mol%), pivalic acid (4.1 mg, 0.04 mmol, 30 mol%) and cesium carbonate (65 mg, 0.2 mmol, 1.5 equiv) in mesitylene (2.62 mL). The two chambers system was reacted for 18h at 120 °C. The crude mixture was purified by flash chromatography using first cyclohexane to elute mesitylene and then cyclohexane/EtOAc (75:25 to 0:1) as eluent., to provide oil **2a** (30.5 mg, 0.114 mmol, 86 %, e.r.: 86:14).

^{1}H NMR (400 MHz, Chloroform-*d*) : δ = 6.11 (s, 2H), 4.57 (d, *J* = 13.9 Hz, 1H), 4.13 (d, *J* = 13.8, 1H), 3.81 (s, 9H), 3.41 – 3.33 (m, 1H), 2.90 (dd, *J* = 14.2, 4.9 Hz, 1H), 2.38 (dd, *J* = 14.2, 2.2, 1H), 1.17 (d, *J* = 6.0 Hz, 3H).

^{13}C NMR (Chloroform-*d*, 101 MHz) : δ = 166.5, 161.2, 159.7, 104.6, 90.3, 55.8, 55.5, 47.0, 43.8, 32.4, 18.7. **IR (neat):** ν = 2946, 1739, 1600, 1140cm^{-1}. **HRMS** (ESI): Calculated for $C_{14}H_{19}NNaO_4$ ([M+Na]$^+$): 288.1206; found: 288.1208

17.03.2017 14:20:51 Page 1 / 1

SHIMADZU LabSolutions **Analysis Report**

<Sample Information>

Sample Name	: rr0792		
Sample ID	:		
Data Filename	: rr0792-run-col3-IA002.lcd		
Method Filename	: Run-col3-IA_90_10_1mL_15min.lcm		
Batch Filename	: Batch rr791 rr792.lcb		
Vial #	: 1-17	Sample Type	: Unknown
Injection Volume	: 10 uL		
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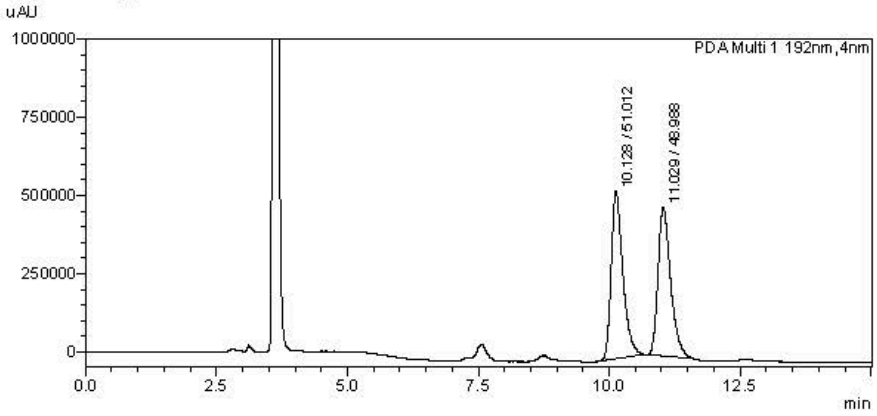

<Peak Table>

PDA Ch1 192nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	10.128	51.012	8250348	533370	0.000		M
2	11.029	48.988	7922978	474718	0.000		M
Total		100.000	16173327	1008088			

D:\Data\David D\rr0792-run-col3-IA002.lcd

SHIMADZU LabSolutions **Analysis Report**

<Sample Information>

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Sample ID	:		
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Method Filename	: Run-col3-IA_90_10_1mL_15min.lcm		
Batch Filename	: RR715-1.lcb		
Vial #	: 1-76	Sample Type	: Unknown
Injection Volume	: 10 uL		
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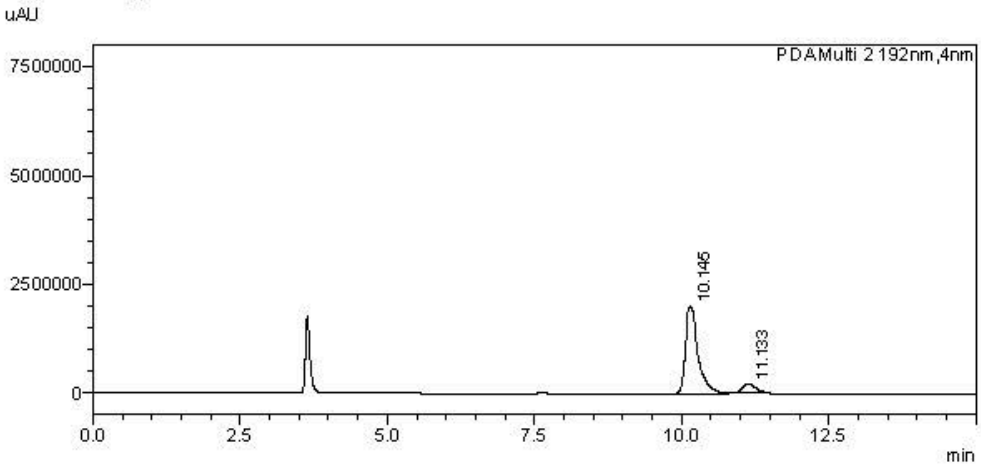


<Peak Table>

PDA Ch2 192nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	10.145	91.625	29842276	2009485	91.625		M
2	11.133	8.375	2727663	187589	8.375		M
Total		100.000	32569939	2197073			

Name

D:\Data\David D\scaleup-run-col3-IA.lcd

(*R*)-4-Methylazetidin-2-one (+)-4.21

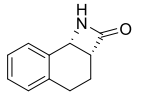
Chemical Formula: C_4H_7NO
Exact Mass: 85.0528

4-methyl-1-(2,4,6-trimethoxybenzyl)azetidin-2-one (135 mg, 0.509 mmol, 1 equiv), $K_2S_2O_8$ (275 mg, 1.02 mmol, 2 equiv) and $Na_2HPO_4.7H_2O$ (273 mg, 1.02 mmol, 2 equiv) were stirred for 3h at 80 °C in MeCN/H_2O [2:1] (18 mL). Then, the crude mixture was dried over $MgSO_4$, filtered and evaporated. The residue was purified by chromatography on silica gel using AcOEt/EtOH [95:5] as eluent to provide (*R*)-4-methylazetidin-2-one **4a** (33 mg, 0.388 mmol, 76 %) as a yellowish oil.

^{1}H NMR (250 MHz, Chloroform-*d*) δ = 5.89 (br s, 1H), 3.83 – 3.73 (m, 1H), 3.11 (ddd, *J* = 14.7, 5.0, 2.1 Hz, 1H), 2.55 (ddd, *J* = 14.8, 2.4, 1.5 Hz, 1H), 1.36 (d, *J* = 6.1 Hz, 3H). **^{13}C NMR (63 MHz, Chloroform-*d*)** δ = 168.2, 45.1, 44.0, 21.3. **IR (neat):** ν = 1739, 1381, 908, 728 cm^{-1} **$[\alpha]_D^{20}$** = +2.8° (c = 1.14, $CHCl_3$); lit. +3.6 (c = 2.3, $CHCl_3$).

The physical and spectroscopic properties matched those described in the literature[197].

(–)-**2a,3,4,8b-Tetrahydronaphtho[1,2-b]azet-2(1*H*)-one (-)-4.23**

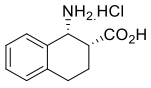


Chemical Formula: $C_{11}H_{11}NO$
Exact Mass: 173.0841

Compound (–)-**2ac** (95 mg, 0.269 mmol, 1 equiv), $K_2S_2O_8$ (145 mg, 0.538 mmol, 2 equiv) and $Na_2HPO_4.7H_2O$ (144 mg, 0.538 mmol, 2 equiv) were stirred for 3h at 80 °C in MeCN/H_2O [2:1] (9.4 mL). Then, the crude mixture was filtered through a pad of $MgSO_4$, and rinsed with MeCN. The filtrate was then treated with NBS (52.7 mg, 0.296 mmol, 1.1 equiv) and TMSCl (3.5 mL, 0.0269 mmol, 0.1 equiv) and stirred for 30 min. The crude mixture was then evaporated and purified by chromatography on silica gel using DCM/MeOH 99:1 as eluent to provide oil compound **4ac** (42 mg, 0.245 mmol, 91 %).

^{1}H NMR (250 MHz, Chloroform-*d*) δ = 7.27 – 7.06 (m, 4H), 6.21 (s, 1H), 4.59 (d, *J* = 5.0 Hz, 1H), 3.65 – 3.59 (m, 1H), 2.83 – 2.57 (m, 2H), 2.28 – 2.17 (m, 1H), 1.69 – 1.42 (m, 1H). **^{13}C NMR (63 MHz, Chloroform-*d*)** δ = 170.8, 139.4, 134.1, 129.7, 129.1, 128.5, 126.6, 51.5, 50.6, 26.9, 23.0. **HRMS** (ESI): Calculated for $C_{11}H_{11}NNaO$ ($[M+Na]^+$): 196.0733; found: 196.0731 **Optical rotation :** $[\alpha]_D^{20}$ = -89.3° (c = 1.0, $CHCl_3$) The physical and spectroscopic properties matched those described in the literature[178].

(1*R*,2*R*)-1-Amino-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid hydrochloride (+).4.24



Chemical Formula: $C_{11}H_{14}ClNO_2$
Exact Mass: 227.0713

Following a methodology from F. Fulöp *et al.*, compound **4ac** was refluxed for 3h in an aqueous HCl solution (2 mL, 6M). The solvent was removed under vacuum to provide oil compound **5ac** as a yellowish solid (32 mg, 0.139 mmol, 100 %).

^{1}H NMR (250 MHz, D_2O) δ = 7.42 – 7.24 (m, 4H), 4.82 (d, *J* = 3.5 Hz, 1H), 3.19 (dt, *J* = 12.0, 3.5 Hz, 1H), 3.10 – 2.91 (m, 2H), 2.37 – 2.23 (m, 1H), 2.15 – 1.95 (m, 1H). **^{13}C NMR (101 MHz, D_2O) δ =** 176.8, 136.6, 130.0, 129.7, 129.5, 128.8, 126.6, 49.5, 41.3, 27.0, 20.2. The physical and spectroscopic properties matched those described in the literature[178].

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